Supreme Court, U.S.
FILED

(1) 97 1880 FEB 20 1998

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No. 97-

IN THE

Supreme Court of the United States

OCTOBER TERM, 1997

ELI LILLY AND COMPANY,

Cross-Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

Cross-Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

CONDITIONAL CROSS-PETITION FOR A WRIT OF CERTIORARI

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118 pp

QUESTIONS PRESENTED

1. Should scientists who conduct cloning experiments in knowing violation of applicable federal safety guidelines, and then misrepresent the origin of their work to the public, the United States Patent and Trademark Office ("PTO"), the United States Senate, and the federal courts, in an attempt to conceal the safety violation, be entitled to enforce patent rights obtained from the illicit invention or should such an incentive to violate the safety regulations be removed by applying the doctrines of unclean hands and inequitable patent procurement to bar enforcement of such patents?

2. Is the fact that a cloning invention was made in violation of applicable federal safety regulations, but knowingly and intentionally described falsely in the examples of a patent application as having been lawfully performed, sufficiently material to warrant refusal to enforce the patent for inequitable patent procurement or unclean hands?

PARTIES TO THE PROCEEDING BELOW

The parties are Petitioner, Eli Lilly and Company, and Respondent, the Regents of the University of California. Eli Lilly and Company possesses neither a parent company nor any non-wholly owned subsidiaries.

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OPINIONS BELOW

A Petition for a Writ of Certiorari filed by the Regents of the University of California ("UC") was docketed in this case on January 21, 1998, and a Brief in Opposition to that petition is being filed concurrently herewith by Eli Lilly and Company ("Lilly"). The opinion of the Federal Circuit is attached as Appendix A to UC's petition and the opinion of the district court is attached as Appendix A hereto.

JURISDICTION

The judgment of the court of appeals was entered on July 22, 1997. The court of appeals denied Lilly's timely petition for rehearing and suggestion for rehearing in banc on October 24, 1997. Jurisdiction of the district court was based on the exclusive federal jurisdiction over patent cases and on federal question jurisdiction. 28 U.S.C. §§ 1338(a), 1331. The jurisdiction of this Court is invoked pursuant to 28 U.S.C. § 1254(1). UC's petition for a writ of certiorari was docketed on January 21, 1998 and Lilly's Conditional Cross-Petition for Certiorari has been filed within the time period prescribed by Sup. Ct. R. 12.5.

CONSTITUTIONAL AND STATUTORY PROVISIONS

There are no Constitutional or statutory provisions involved within the meaning of Sup. Ct. R. 14.1(f).

STATEMENT OF THE CASE

Lilly refers this Court to the "Statement of the Case" set forth in Lilly's Brief in Opposition to UC's petition for a writ of certiorari, filed concurrently herewith, for a full discussion of the procedural history of the litigation brought by UC against Lilly for alleged infringement of United States Patents

4,652,525 ("the '525 patent) and 4,431,740 ("the '740 patent"). The patents relate to the cloning of DNA encoding insulin. UC's petition before this Court raises a number of issues regarding venue. The subject matter of this conditional cross-petition, however, relates to the circumstances surrounding UC's procurement of its '525 patent–circumstances which raise public policy issues that are as important today as they were twenty years ago when UC began its cloning experiments.

The purported cloning of a sheep named Dolly has triggered waves of fear and anxiety among scientists, politicians, pundits, and ethicists about the possibility of engaging in the cloning of human beings. In response to such concerns, President Clinton noted that "[s]cience often moves faster than our ability to understand its implications[;] [t]hat is why we have a responsibility . . . to harness the powerful forces of science and technology so that we can reap the benefit while minimizing the potential danger."[1] For this reason, the President issued a directive "that bans the use of any Federal Funds for any cloning of human beings." *Id.* Indeed, the United States Senate is currently debating legislation that would seriously curtail such research. Not surprisingly, commentators have raised "hypothetical" concerns about the potential ramifications of a scientist in this country carrying out such radical experiments in the face of the potential safety and ethical issues.[2] Because U.S. patent rights are bestowed upon the first inventor, the prospect of securing patent rights on the

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[1] Remarks Announcing the Prohibition on Federal Funding for Cloning of Human Beings and an Exchange with Reporters, 33 Weekly Comp. Pres. Doc. 278 (March 4, 1997).

[2] Rich Weiss, *Clinton Presses Ban on Human Cloning*, Wash. Post, January 11, 1998, at A06.

fruit of cloning experiments creates a powerful incentive to conduct such experiments prematurely in violation of regulations and limitations on such research intended to protect the public.

These concerns are *not* hypothetical. In this case, the United States District Court for the Southern District of Indiana specifically found that UC, in order to secure patent rights in connection with cloning of insulin genes now embodied in the '525 patent, violated precisely analogous safety regulations of the National Institutes of Health ("NIH") promulgated to protect the public from the then unknown risks of the emerging field of cloning DNA. (App. A at 67.) The trial court found further that UC then misrepresented the origins of the cloned DNA sequence information to the public, to the PTO, to the United States Senate, and to the district court itself, all in an apparent attempt to conceal the underlying safety violation. *Id.* at 62-79.

At the time that the alleged invention of the '525 patent was made, there was significant public concern and a serious, ongoing public debate over the safety of cloning recombinant DNA–not unlike the current debate over the cloning of human beings. *Id.* at 62. Concerns about safety had prompted scientists to impose a voluntary moratorium on recombinant DNA research in 1975. *Id.* In June of 1976, the NIH promulgated guidelines regulating the conditions under which recombinant DNA experiments could be conducted. *Id.* at 62-63. The NIH guidelines explicitly applied to research conducted using federal funds, including the work of UC underlying its application for the '525 patent. *Id.* at 64.

The guidelines specified degrees of "physical containment" required for conducting certain classes of

experiments and also specified which "plasmids" or "vectors" could be used for these experiments. *Id.* at 62-63. The only two plasmids originally certified by the NIH for use were called "pSC101" and "pCR1." *Id.* at 64. Neither was particularly easy to use. A somewhat more useful plasmid called "pMB9" was certified as safe by the NIH on April 18, 1977. *Id.* at 64. A very powerful plasmid called "pBR322" was not certified as safe by the NIH until July 7, 1977. *Id.* at 64.

No later than May 9, 1977, within weeks after certification of the plasmid pMB9, UC submitted a manuscript to the journal *Science* purporting to describe the isolation of four pieces of rat insulin "complementary DNA" ("cDNA") allegedly isolated using the certified plasmid pMB9. *Id.* at 71. This same work formed the basis for the '525 patent application also filed in May of 1977. *Id.* at 72-74. Yet, in September of 1977, word leaked out to the scientific press that the UC researchers had in fact performed an earlier rat insulin experiment with the then *uncertified* plasmid pBR322. *Id.* at 68. According to the public account of the events at that time, the UC researchers had used pBR322 in the mistaken belief that it had been certified but, upon learning of their error, destroyed the experiment before any insulin DNA sequence information was derived. *Id.* at 68-69.

Upon seeing reports of the pBR322 experiment in the press, the NIH asked for an explanation from UC. Dr. Rutter, an inventor named on the '525 patent, was also asked to testify at Senate hearings in November of 1977 considering federal safety legislation to regulate recombinant DNA research. Unsatisfied with Dr. Rutter's explanation of the incident, the Senate requested further information from the NIH, which in turn requested further information from UC. UC responded to

the NIH on January 20, 1978, and its response was passed on to the Senate. *Id.* at 69.

UC represented that: (1) it had performed the pBR322 experiment beginning in mid-January of 1977 in the mistaken belief that pBR322 had been approved; (2) that Dr. Howard Goodman, the head of the laboratory where the work was conducted and also a coinventor on the '525 patent, learned for the first time on March 1, 1977, that pBR322 had not been certified; (3) Goodman ordered, at a meeting of the laboratory on March 3, 1977, all further work with the pBR322 clones be stopped; (4) the clones were destroyed on March 19, 1977; and (5) the experiment was repeated with the pMB9 plasmid, which yielded a small number of clones that were reported in the published *Science* article and original application for the '525 patent.

However, after a full and fair trial on the merits, the Southern District of Indiana found that the evidence presented at trial portrayed a far different version of the factual circumstances surrounding UC's isolation of rat insulin DNA. The district court found by clear and convincing evidence that UC *violated* the applicable regulatory guidelines governing the safety of recombinant DNA technology by using the uncertified pBR322 plasmid to clone the DNA sequence for rat insulin and then intentionally *misrepresented* the origins of this data to the public, to the PTO0 in order to obtain the '525 patent, to the United States Senate, which was considering legislation regulating such recombinant DNA experiments, and to the district court itself in an apparent attempt to conceal this safety violation. *Id.* at 64 n.47, 71, 74, 76-78.

While UC contends that it initiated rat insulin DNA experiments using pBR322 in January 1977 in the mistaken

belief that the plasmid had been approved, the trial court found that by February 4, 1977, the two scientists most closely involved with the experiments—Drs. Axel Ullrich and John Shine (both coinventors on the '525 patent)—were informed at a laboratory meeting that pBR322 had *not* been certified for use. *Id.* at 65-66. UC, however, *continued* to pursue its rat insulin DNA experiments using pBR322. *Id.* at 66-67. Indeed, UC's own biosafety committee admitted that there was "no satisfactory explanation" for this conduct, conduct which the district court found constituted a knowing, willful violation of the NIH guidelines. *Id.* at 67.

Moreover, although UC specifically informed the NIH that the pBR322 clones were destroyed on March 19, 1997,[3] the evidence at trial clearly demonstrated that Ullrich continued to use the purified DNA and that both Rutter and Goodman were aware that he did. *Id.* at 67-71. In this regard, Drs. Rutter and Goodman exchanged on March 22 and March 25, 1977, respectively, both several days after the alleged destruction of the illicit pBR322 clones, ***registered letters*** in which they admitted that the pBR322 DNA had *not* been destroyed but had been *saved* for further sequencing. *Id.* at 69-71.

In the registered letters, Goodman and Rutter admitted that they decided to "[k]eep the cloned DNA since the experiments had already been performed . . . We believed that further sequencing of the DNA clones was acceptable since the hypothetical danger, if any, is not with the DNA itself." *Id.* at 69. Although both Goodman and Rutter testified at trial that the letters were inaccurate, the district court found "Rutter and Goodman's trial testimony regarding the letters *not credible*," stating that "[t]hese 'smoking gun' letters could have had no

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[3] *Id.* at 69.

purpose but to keep either of the writers from attributing the misuse to the other." *Id.* at 69-70 (emphasis added).

Furthermore, the district court, relying in part on the expert analysis of UC's laboratory notebooks and manuscripts at issue by a Nobel prize winning molecular biologist, found that UC had not repeated the cloning experiments with the pMB9 plasmid as reported to the NIH, the Congress, and the PTO, but had instead used the data from the *pBR322* experiments in both the *Science* manuscript and the '525 patent. *Id.* at 72-74. The court stated that "we find that the duplications in the structure of pBR322-derived clones and the structure of clones reported in the *Science* manuscript and the original '525 patent application are not products of random chance. Rather, we find that UC researchers used data derived from the pBR322 experiments in the aforementioned publications." *Id.* at 74.

The district court also specifically commented on Rutter's testimony before the United States Senate. *Id.* at 74-75. The Senate was concerned that commercial interest or a profit motive was associated with the use of the unapproved plasmid. Although Dr. Rutter assured the Senate that no commercial interests were involved, the court found that the record demonstrated otherwise. *Id.* at 64 n.47, 75-77. On March 9, 1977—mere days after learning that insulin DNA had been isolated in an uncertified plasmid—Howard Goodman called Lilly. *Id.* at 75. Goodman came to Lilly on March 14, 1977, soliciting "money for lab" and "consulting." *Id.* When asked by Lilly "what plasmid?" Goodman answered "can't say." *Id.* On March 12, 1977, Goodman met with Genentech and was offered "[m]oney for salaries . . . shares [of stock] . . . [and] consulting." *Id.* at 76. On March 13, 1977, Goodman called Genentech. *Id.* at 76. His notes of the call state "'Hinted' [at]

we were bringing something very valuable to the co. & should be compensated for -- difference in kind between 'idea' & having [it]." *Id.* at 76. Then, on or about March 15, 1977, Goodman called Genentech, stating: "Problem that in Boyer plasmid. Lay low. Not approved. Can't apply for patent yet."[4] *Id.* Accordingly, and contrary to Dr. Rutter's Congressional testimony, the court found "that continued use of the fruits of the pBR322 research was driven by commercial interests and we find that those commercial interests were tied closely to Genentech." *Id.* at 76-77. Indeed, the court noted that the inventors of the '525 patent were entitled to fifty percent of the net profits received from royalties derived from licensing the '525 patent. *Id.* at 77 n.56.

Regarding the relationship between the illicit pBR322 clones and the application for the '525 patent, the trial court found that, contrary to representations made to the U.S. Senate, the '525 patent disclosure was in fact based on the pBR322 data. *Id.* at 78. The examples of the patent application, however, falsely stated that the experiment had been done using the certified vector pMB9. *Id.*

The district court found that these misrepresentations associated with UC's unauthorized experimentation with the pBR322 plasmid and the subsequent attempts to conceal the safety violation were intentional and material to the patentability of the '525 patent. Relying on the specific teachings of this Court set forth in *Precision Instruments Manufacturing Co. v. Automotive Maintenance Machinery Co.*, 324 U.S. 806, 816 (1945), the trial court held that these

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[4] The district court found that the "Boyer plasmid" refers to pBR322, which had been developed in Dr. Boyer's laboratory.

misrepresentations rendered the '525 unenforceable. (App. A at 78-80.) Based on the district court's opinion and due to the extraordinary amount of resources expended by Lilly to defend against five years of litigation based on patents procured through inequitable conduct, Lilly filed a motion before the district court to recover its reasonable attorney fees, alleging that the instant case is "exceptional" within the meaning of 35 U.S.C. § 285.

Before the district court ruled on Lilly's attorney fee motion, the Federal Circuit—while affirming the district court's decision that the '525 patent was invalid—reversed the district court's determination that the patent was procured through inequitable conduct. (UC Pet. App. A at 23.) In so doing, the Federal Circuit *did not* disturb any of the district court's factual findings regarding UC's misrepresentations. The Federal Circuit instead held as a matter of law that such misrepresentations were not *material* to the patentability of the '525 patent and thus could not constitute inequitable patent procurement. *Id.* It was the apparent view of the Federal Circuit that the misrepresentations were "immaterial" because there was no technical ground of unpatentability under which the PTO could have rejected UC's patent application claims even had the PTO been informed of the true illicit origin of the data upon which the patent application was based.

The Federal Circuit also rejected Lilly's alternative assertion that the '525 patent was unenforceable under the doctrine of unclean hands. *Id.* at 25. The court stated that the doctrine of "unclean hands" could not render a patent unenforceable without proof of materiality because such a "categorization is inconsistent with this court's view that materiality is a necessary ingredient of any inequitable conduct." *Id.* at 25-26.

Lilly now seeks review by this Court of the Federal Circuit's reversal of the trial court's holding that the '525 patent is unenforceable. As will be discussed in greater detail below, this part of the Federal Circuit's decision is contrary to direct precedent of this Court, is inconsistent with other decisions of the Federal Circuit, represents profoundly unwise public policy, and touches upon a matter of significant current importance to the country. The fundamental question raised by this petition is whether the economic rewards of the patent system are to be bestowed upon those who knowingly violate applicable federal safety regulations regarding cloning in order to secure an advantage over their competitors who do obey the rules.

REASONS FOR GRANTING THE WRIT

I. THE FEDERAL CIRCUIT FAILED TO APPLY THE DOCTRINE OF UNCLEAN HANDS TO A SITUATION WHERE THE ACT OF INVENTION WAS TAINTED WITH INEQUITY

In reversing the district court's determination that the '525 patent was unenforceable, the Federal Circuit held that the doctrine of unclean hands does not apply *unless* intentional misrepresentations made by the applicant are material to the patentability of the claimed subject matter. (UC Pet. App. A at 24-25.) Because the Federal Circuit believed that a reasonable patent examiner would not have considered "non-compliance with the NIH guidelines to be material to patentability," the Federal Circuit refused to apply the doctrine of unclean hands to bar enforcement of the '525 patent. *Id.* This decision, however, is contrary to the precedent of this Court and could have serious and profound legal and safety implications for the entire country if allowed to stand.

The applicability of the doctrine of unclean hands to patent owners seeking relief in federal court was established by this Court more than sixty years ago in *Keystone Driller Co. v. General Excavator Co.*, 290 U.S. 240 (1933). The Court held that application of the doctrine is not "bound by formula or restrained by any limitation that tends to trammel the free and just exercise of discretion." *Id.* at 245-46. Likewise, in *Precision Instrument Manufacturing Co. v. Automotive Maintenance Machinery Co.*, 324 U.S. 806, 814 (1945), the Court specifically observed:

> The guiding doctrine in this case is the equitable maxim that "he who comes into equity must come with clean hands." This maxim is far more than a mere banality. It is a self-imposed ordinance that closes the doors of a court of equity to one tainted with inequitableness or bad faith relative to the matter in which he seeks relief, however improper may have been the behavior of the defendant.

In fact, the Court in *Precision Instrument* applied the doctrine of unclean hands to deny relief to a patentee who has acted inequitably in its dealings with the PTO. The Court observed that because a patent "is affected with a public interest," "the public [has] a paramount interest in seeing that patent monopolies spring from backgrounds free from fraud or other inequitable conduct." *Id.* at 816. This principle led the Court to hold that patent applicants owe to the PTO an "uncompromising duty" of candor. *Id.* at 818; see *also Hazel-Atlas Glass Co. v. Hartford-Empire Co.*, 322 U.S. 238, 246 (1944)("The public welfare demands that the agencies of

public justice be not so impotent that they must always be mute and helpless victims of deception and fraud.")

Thus, the prior decisions of this Court strongly indicate that the doctrine of unclean hands should be applied under the circumstances presented, as here, where an applicant for a patent made its invention by knowingly violating federal safety regulations promulgated by the NIH and then misrepresented the origins of the resulting data to the PTO, the United States Senate, and the courts. Indeed, it is situations such as the instant case where it is critically important that courts apply the doctrine of unclean hands to discourage such activities. If the immense economic reward that attends the issuance of an enforceable U.S. patent is to be bestowed upon the first successful experimenter regardless of the legality of the experimentation, a tremendous and profoundly harmful incentive is created to violate laws and regulations governing scientific research promulgated for the protection of the public.

The Federal Circuit suggests that if it were to apply the doctrine of unclean hands in the instant case without finding that the intentional misrepresentations were "material to patentability," it would eliminate the "materiality" component from the standard inequitable conduct analysis. Lilly, however, does not advocate such a broad rule. Instead, Lilly merely asserts that where, as here, the very act of invention is tainted with inequity, and the patent applicant has sought to conceal that inequity through misrepresentations made to the legislative branch (the United States Senate), the judicial branch (the Southern District of Indiana), and the executive branch (the PTO and NIH) of the federal government, a court should not be *required* to enforce the resulting patent even if the subject matter it claims would otherwise be patentable.

Because this Court has stated that the applicability of the doctrine of unclean hands is not the prisoner of a set formula, the concept of materiality must be broad enough to encompass those unsanctionable breaches of conscience in connection with a transaction being reviewed by the PTO or the Court which are "offensive to the dictates of natural justice. . . ." *Keystone Driller*, 290 U.S. at 245. UC's conduct in this case falls squarely into this category.

For the foregoing reasons, Lilly respectfully submits that UC's misrepresentations with respect to the '525 patent are sufficiently inequitable and deceitful to warrant refusal by a United States court to enforce the resulting patent under the doctrine of unclean hands in accordance with applicable precedent of this Court. Accordingly, this Court should grant certiorari to review this part of the Federal Circuit's decision.

II. THE FEDERAL CIRCUIT IMPROPERLY APPLIED THE DOCTRINE OF INEQUITABLE PATENT PROCUREMENT

A. The Federal Circuit Improperly Held That Only Misrepresentations Bearing On Patentability Are Material To An Inequitable Conduct Analysis

To establish the defense of inequitable patent procurement, an accused infringer must establish by clear and convincing evidence that nondisclosed or misrepresented information was *material,* that the applicant knew of the withheld information and its materiality, and that it was withheld with the *intent* to mislead the PTO. *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995); *Kingsdown*

Medical Consultants, Ltd. v. Hollister Inc., 863 F.2d 867, 872 (Fed. Cir. 1988). The Federal Circuit's decision in the instant case, however, misapprehends the scope of *misrepresented* information which could be recognized as "*material*" in an inequitable patent procurement analysis.

Specifically, the Federal Circuit concluded that UC's conduct cannot render the '525 patent unenforceable for "inequitable conduct"because the true origin of the rat insulin cDNA sequence data disclosed in the '525 patent was not "important to the patentability of a claim" (UC Pet. App. at 23-25.) This conclusion was apparently based on a legally incorrect paraphrase of the definition of materiality stated in *J.P. Stevens & Co., Inc. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1559 (Fed. Cir. 1984). *J.P. Stevens* did not, however, narrowly restrict the concept of materiality in the context of *misrepresentations* to technical patentability defects in the manner suggested by the Federal Circuit. Instead, *J.P. Stevens* defined materiality in terms of "whether there is a substantial likelihood that a reasonable examiner would have considered the . . . false information important in deciding whether to allow the application to issue as a patent." *Id.* at 1559.

At the time of the conduct here at issue, the PTO had asserted the authority, sanctioned by precedent from the Federal Circuit's predecessor, to refuse to issue a patent on any ground which would render the patent unenforceable in court. *Norton v. Curtiss*, 433 F.2d 779, 792 (C.C.P.A. 1970). Thus, the scope of misrepresentations which the PTO could have regarded as important in deciding whether or not to issue a patent must have been just as broad as the conduct of which a court could have taken note in refusing to enforce a patent for unclean hands. As previously demonstrated, the latter is clearly *not* strictly limited to technical patentability defects but must be

broad enough to encompass unsanctionable breaches of conscience of the sort in which UC has here engaged.[5]

B. The Federal Circuit Erred In Concluding That UC's Misrepresentations Were Not Material To Patentability

Even if materiality to technical patentability were required, it is apparent that UC's misconduct had a series of immediate effects on its application for the '525 patent. First, UC secured an earlier filing date (May 1977) and earlier processing of its application than it would had it been required to await the certification of pBR322 before commencing its work. This was precisely the illicit benefit secured by the patentee in *General Electro Music Corp.* through misrepresentations about the conduct of a pre-examination search in a petition seeking expedited patent examination. UC's misrepresentation here was at least as "material to patentability" as the misrepresentation in *General Electro Music.*

"Materiality" is further illustrated by the fact that, had UC been restricted to its April 1978 continuation-in-part filing date (the first filing date following certification of pBR322),

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[5] In this regard, the Federal Circuit's prior decision in *General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405 (Fed. Cir. 1994), made abundantly clear that misrepresentations considered important by an examiner in deciding whether to allow the application to issue as a patent encompass a field far wider than strict patentability defects. The Federal Circuit there refused to enforce a patent where the applicant intentionally submitted a false statement regarding whether a pre-examination search had been conducted.

Genentech's U.S. Patent No. 4,704,362, with an original filing date in November 1977, would have been potentially patent-defeating prior art to the '525 patent under 35 U.S.C. § 102(e).[6] UC's false examples describing the results of the illicit pBR322 experiment as having been obtained using the certified vector pMB9 also concealed a possible "best mode" violation[7] of the sort recognized by the PTO as material to its examination processes in cases such as *Steierman v. Connelly*, 192 U.S.P.Q. 433 (PTO Bd. of Pat. Int. 1975) (discovery of false example led to discovery of best mode violation). The false example, falsely describing successful conduct of the experiment with the much inferior pMB9 plasmid, also concealed from the PTO examiner a possible "enabling disclosure" defect.[8] Finally, the

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[6] Section 102(e) precludes issuance of a patent on a invention described in a U.S. patent issued to another with an earlier filing date.

[7] 35 U.S.C. § 112, first paragraph, requires that the inventor discloses in his or her patent application "the best mode contemplated by the inventor of carrying out his invention." Failure to do so is grounds for rejecting the affected patent application claims.

[8] The patent statute, 35 U.S.C. § 112, first paragraph, requires the application to include a disclosure of the invention sufficient "to enable any person skilled in the art . . . to make and use the same. . . ." Failure to do so is grounds for rejecting the affected patent application claims. The power of pBR322 lay in its dual selectable antibiotic resistance genes for ampicillin resistance and tetracycline resistance, with which the number of microorganism cultures that had to be screened for cDNA inserts of interest could be reduced to manageable levels. In contrast, pMB9 had only one selectable antibiotic resistance gene (tetracycline resistance) and a second gene for "colicin immunity." The record shows that "colicin

(continued...)

false example prevented the PTO from making the policy determination which UC obviously most feared—whether violation of the federal safety regulations governing recombinant DNA research should preclude issuance of a patent to the transgressor on the illicit fruit flowing from the violation.

The Federal Circuit, nonetheless, dismissed UC's misrepresentation as immaterial because the Federal Circuit *assumed* that pMB9, even if not actually used, was not "inoperable in the stated examples." (UC Pet. App. A at 23). This conclusion is unwarranted by the evidence before the Federal Circuit. The very fact that UC repeatedly used the data from the illicit pBR322 experiments in its patent application and scientific publication belies the Federal Circuit's assumption that the experiment could have been done using pMB9. Indeed, there is no evidence in the record that rat insulin cDNA was ever *independently* isolated by UC, i.e., without use of the pBR322 DNA, using pMB9.

The Federal Circuit also assumed that the pMB9 experiment described in Examples 4 and 5 of the '525 patent could just as easily have been stated as a "hypothetical" example. (UC Pet. App. A at 23-24). This assumption is also incorrect. Example 6 of the '525 patent is a true hypothetical example purporting to describe how a *human* insulin cDNA

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[8](...continued)
immunity" was not an effective means for selecting microorganisms containing cDNA of interest. Indeed, UC specifically tried and failed to repeat the pBR322 experiment in another certified plasmid "pCR1" which also contained a colicin immunity gene. It is, therefore, to be doubted that the false example using pMB9 in the '525 patent would actually have been an enabling disclosure.

might be isolated, although there is no evidence in the record that anybody was ever able to use the disclosed technique to isolate human DNA. What distinguishes this *hypothetical* Example 6 from what are described as *actual* experiments in Examples 4 and 5 is that *no* cDNA sequence information was available for the hypothetical human experiment whereas detailed rat insulin cDNA sequence data is given in Example 5. Such sequence data could only have been determined by actual experiment. The record is abundantly clear that, due to the redundancy in the genetic code, there is no way the actual insulin cDNA sequence (rat or human) could have been hypothetically divined.

The fact that Examples 4 and 5 purported to be real experiments yielding real sequence data turns out to be what distinguishes what the Federal Circuit found to be a legally adequate description supporting UC's claims to *rat* insulin cDNA from the legally inadequate description alleged to support UC's claims to *human* and other vertebrate insulin cDNA. (UC Pet. App. A at 14-15). The examples could not have been and were not hypothetically stated. The examples were falsely stated as real experiments which, the record shows, were not conducted as described. UC's conduct was, therefore, in direct conflict with the PTO's mandate in § 2004 of the Manual of Patent Examining Procedure not to use false examples.[9]

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[9] This fact distinguishes the present case from *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1578 (Fed. Cir. 1984), cited by the Federal Circuit. The examples at issue in that case were found by the trial court to have been written in the present tense to conform with the PTO requirements on prophetic examples. *Id.*

In view of the foregoing, there was ample relationship between UC's intentionally false representation regarding the origins of its rat insulin cDNA sequence data, which formed the basis for the description of the only patentable invention described in the '525 patent, and the examination processes of the PTO. That relationship, which was misapprehended by the Federal Circuit, established the "materiality" of UC's misrepresentation.

UC's very act of invention was infected with inequity and deceit. The invention was made in knowing violation of the applicable federal safety regulations promulgated to protect the public from the as yet unknown dangers of recombinant DNA research. The violation afforded UC a substantial unfair competitive advantage in relation to other researchers who obeyed the regulations. UC's conduct is analogous to that of Rosa Ruiz who, after illicitly riding the subway over a portion of the course, claimed to have won a marathon race. Moreover, UC's misrepresentations allowed it to avoid inquiry into the propriety of its original patent application filing date. In this regard, there is no doubt as to what would have happened to UC's application for the '525 patent had the Senate been truthfully advised that it was based on the illicit pBR322 data. Accordingly, Lilly submits that, UC's conduct must be regarded as a matter which a reasonable examiner would have regarded as important in deciding whether to issue the application for the '525 patent. It is, therefore, "material" under applicable Federal Circuit authority. Because the Federal Circuit's decision represents a departure from well-established authority and sound public policy, Lilly submits that this Court should grant certiorari to rectify this error.

CONCLUSION

For the foregoing reasons, Lilly respectfully petitions that this Court grant Lilly's conditional cross-petition for certiorari.

Respectfully submitted,

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Appendix

APPENDIX A

University of California
v.
Eli Lilly and Co.

U.S. District Court Southern District of Indiana

MDL Docket No. 912 No.
IP-92-0224-C-D/G

Decided December 11, 1995

Arthur I. Neustadt, Jean-Paul Lavalleye, Marc R. Labgold, and William J. Healey, of Oblon, Spivak, McClelland, Maier & Neustadt, Arlington, Va.; Susan B. Tabler, of Ice, Miller, Donadio & Ryand, Indianapolis, Ind.; Gerald P. Dodson and Emily A. Evans, of Arnold, White & Durkee, Palo Alto, Calif., for plaintiff.

Donald R. Dunner, Charles E. Lipsey, and Mark W. Lauroesch, of Finnegan, Henderson, Farabow, Garrett & Dunner, Washington, D.C.; Jerry E. Hyland and Jan M. Carroll, of Barnes & Thornburg, Indianapolis; Amy E. Hamilton, Indianapolis, for Eli Lilly & Co.

John E. Kidd and Maurice N. Ross, of Rogers & Wells, New York, N.Y.; Hugh E. Reynolds Jr. and David T. Kasper, of Locke, Reynolds, Boyd & Weisell, Indianapolis, for Genetech Inc.

Dillin, S.J.

Heretofore, from August 21 through September 1, 1995, the Court heard a bench trial of this action. Post-trial briefs were filed in lieu of closing arguments, the last of which were filed October 27, 1995. Having heard the evidence, considered the briefs, and being duly advised, the Court now makes its findings of fact and conclusions of law in the form of this Memorandum of Opinion.

Background

This case was initiated when the Regents of the University of California (UC) filed a patent infringement action against Eli Lilly and Company (Lilly) on February 7, 1990, in the United States District Court for the Northern District of California. UC's Amended Complaint, filed on April 24, 1991 alleges that Lilly's production of recombinant DNA human insulin products willfully infringes three of UC's patents: United States Patent Numbers 4,652,525 (the '525 patent); 4,431,740 (the '740 patent); and 4,440,859 (the '859 patent). After filing its Amended Complaint, UC withdrew its infringement charges arising from the '859 patent, leaving the '525 and the '740 patents at the center of this dispute.

In early 1992, the instant action was one of six cases consolidated in this Court for pretrial proceedings by the Judicial Panel on Multidistrict Litigation. See *In re Recombinant DNA Technology Patent and Contract Litig.*, Docket No. 912 (J.P.M.L. Feb. 19, 1992), aff'd, *In re Regents of the Univ. of Cal.*, 964 F.2d 1128 [22 USPQ2d 1748] (Fed. Cir. 1992); *In re Recombinant DNA Technology Patent and Contract Litig.*, Docket No. 912 (J.P.M.L. Oct. 1, 1993). During the discovery stage of this and the other consolidated actions and on Lilly's motion, this Court transferred cause number IP-92-0224-C to the Southern District of Indiana pursuant to 28 U.S.C. Section 1404(a).

The '525 patent issued to UC on March 24, 1987, for an invention entitled, "Recombinant Bacterial Plasmids Containing the Coding Sequences of Insulin Genes." The named inventors on the patent are Dr. William J. Rutter (Rutter), Dr. Raymond Pictet (Pictet), Dr. John Chirgwin (Chirgwin), Dr. Howard Goodman (Goodman), Dr. Axel Ullrich (Ullrich) and Dr. John Shine (Shine). The '740 patent issued to UC on February 14, 1984, for an invention entitled, "DNA Transfer Vector and Transformed Microorganism Containing Human Proinsulin and Pre-proinsulin Genes." The named inventors on the '740 patent are Dr. Graeme Bell (Bell), Pictet, Goodman and Rutter. Although the '740 patent issued prior to issuance of the '525 patent, the '525 bears an earlier application date than does the '740.

As their titles reflect, the patents in issue in this case involve recombinant DNA technology. Recombinant DNA is "DNA that has been artificially introduced into a cell so that it alters the genotype and phenotype of the cell and is replicated along with the natural DNA."[1] Following is a brief review of the science involved in recombinant DNA technology.

All living things are composed of cells, which can be thought of as microscopic, biological building blocks. Deoxyribonucleic acid (DNA), in various compositions, is found in all living cells. In higher organisms known as eukaryotes, such as humans, DNA is contained within the nucleus of the cell. In lower organisms known as prokaryotes, such as bacteria and algae, DNA is found in the cytoplasm of the cell.

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[1] Dorland's Medical Dictionary (27th ed. 1988).

The DNA molecule contains, in effect, coded instructions for the manufacture of chemicals necessary for life, including proteins such as insulin and growth hormone in humans. The molecular structure of DNA is in the form of a double helix, generally conceptualized as an enormously long, twisted rope ladder. The length and specific structure of DNA corresponds to the complexity of the organism. It is estimated that the human DNA ladder contains several billion "rungs."

Each rung of any DNA molecule consists of a pair of base chemicals (or nucleotides), of which there are only four used to build up DNA molecules -- adenine, thymine, guanine and cytosine. In large part, the varying pattern of these chemicals gives each complete DNA molecule its uniqueness. In addition, each rung in the DNA molecule contains a joint, thereby enabling a rung to be broken by the cell and reattached. Thus, a cell can duplicate its DNA or copy small sections of it.

A section of DNA that contains the coded instructions for the manufacture of a particular protein is called a gene. When the information contained in a particular gene is communicated to other parts of the cell, the cell can produce that protein encoded in the gene.

Scientists have discovered that the form of information in DNA is not unique to a particular species. For example, single cell bacteria can read sections of human DNA when such DNA sections are attached to the bacteria's own DNA and then can produce the chemicals encoded therein.

Molecular biologists and chemists only recently have developed the techniques necessary to isolate a particular human gene, determine its sequence, i.e., its structure, copy or synthesize it, insert it into the DNA of bacteria, and coax the bacteria to follow the gene's directions and express the desired

chemical. Since bacteria replicate very rapidly and the altered DNA of the bacteria is duplicated in the replication process, the production of the desired chemical by bacteria has become commercially feasible.

Significant to this case are three methods for obtaining genes for use in the recombinant production of a desired protein -- in this case, human proinsulin and, ultimately, human insulin. In the first method, messenger RNA (mRNA) is derived from human tissue that produces insulin and subsequently is subjected to a process called reverse transcription.[2] [FN2] Through reverse transcription, copy (or complementary) DNA (cDNA) is obtained, mirroring the DNA encoding proinsulin found in the human source. A second method for obtaining a gene entails a chemical process and results in an artificial (or synthetic) gene. The artificial gene is made in test tubes (in vitro) using a series of repetitive chemical reactions to build up a desired DNA sequence. This desired sequence is determined in advance based on the protein sequence (sequence of amino acid building blocks) of the material one wants the cell to produce. The third method of obtaining a gene involves a combination of the cDNA and artificial DNA methods. Its product is referred to as semisynthetic DNA.[3]

The gene Lilly uses in manufacturing human proinsulin is a semisynthetic segment of DNA. UC contends that Lilly's use of this proinsulin gene in its commercial production of human proinsulin -- a precursor to the protein human insulin used in

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[2] An enzyme called reverse transcriptase is used for this process.

[3] For additional information concerning the science underlying recombinant DNA technology, see *In re O'Farrell*, 853 F.2d 894 [7 USPQ2d 1673] (Fed. Cir. 1988).

the treatment of diabetes -- infringes the '525 patent under the doctrine of equivalents and infringes the '740 patent both literally and under the doctrine of equivalents. Lilly counters not only that it is infringing neither of UC's patents, but also that both the patents are invalid and unenforceable. We will consider such issues in the order named.

I. Infringement

An infringement analysis is a two-step process. First, the court must determine the meaning and scope of the patent claims allegedly infringed. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 [34 USPQ2d 1421] (Fed. Cir.) (citation omitted), *cert. granted*, 116 S. Ct. 40, 132 L. Ed. 2d 921 (1995). This step is often referred to as claim construction or claim interpretation. *Id.* Next, the properly construed claims must be compared to the product or process accused of infringing. *Id.*

UC's charges against Lilly include both literal infringement and infringement under the doctrine of equivalents. UC must prove infringement by a preponderance of the evidence. *Braun, Inc. v. Dynamics Corp. of America*, 975 F.2d 815, 819 [24 USPQ2d 1121] (Fed. Cir. 1992). Literal infringement is established if each and every element of the claim is present in the accused article. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 [19 USPQ2d 1367] (Fed. Cir. 1991).

Moreover, courts long have applied the doctrine of equivalents to protect the substance of the patentee's right to exclude. *Hilton Davis Chemical Co. v. Warner-Jenkinson Co., Inc.*, 62 F.3d 1512, 1517 [35 USPQ2d 1641] (Fed. Cir. 1995), *petition for cert. filed*, 64 U.S.L.W. 3349 (U.S. Nov. 6, 1995) (No. 95-728). In order to avoid infringement under the doctrine of equivalents, an accused product or process "must include

'substantial and not merely colorable' differences from the patent claims."*Id.* (quoting *Singer Mfg. Co. v. Cramer*, 192 U.S. 265, 286 (1904) (further citations omitted)). In *Hilton Davis*, the Federal Circuit held that the "application of the doctrine of equivalents rests on the substantiality of the differences between the claimed and accused products or processes, assessed according to an objective standard."*Id.* at 1518.

The Federal Circuit has stated that the traditional function-way-result test[4] is one measure of the substantiality of the differences between the patented and accused products or processes. However, the court explained, " 'equivalence, in the patent law, is not the prisoner of a formula. . . .' "*Hilton Davis*, 62 F.3d at 1518 (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 [85 USPQ 328] (1950)). The court admonished that the finder of fact must consider all evidence relevant to the substantiality of the differences whether or not such evidence is pertinent to the function-way-result test. *Id.* at 1518-20. The court discussed evidence of copying and evidence of designing around and stated that such evidence may be relevant to the issue of infringement under the doctrine of equivalents. *Id.*

A. The '525 Patent At issue are independent claims one and two of the '525 patent and dependent claims four through seven. In claim one, the inventors claim:

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[4] This test determines the (in)substantiality of the differences between the claimed and accused products or processes by examining if the accused product or process " 'performs substantially the same function in substantially the same way to obtain the same result.' "*Hilton Davis*, 62 F.3d at 1518 (quoting *Sanitary Refrigerator Co. v. Winters*, 280 U.S. 30, 41-42 [3 USPQ 40] (1929)).

A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

UC Ex. 2 at col. 20. Claim two is similar to claim one, but rather than claiming the recombinant plasmid,[5] it claims the microorganism that contains the recombinant DNA. *Id.* at col. 21.

The parties agree that the claims in the '525 describe cDNA, a description embodied in the phrase "reverse transcript of an mRNA." Since Lilly's proinsulin DNA sequence is a semisynthetic sequence rather than cDNA, UC does not allege that Lilly literally infringes the claims of the '525 patent. UC does assert, however, that Lilly's DNA infringes under the doctrine of equivalents. Hence, we must consider if there exist only insubstantial differences between the subject claims of the '525 and Lilly's DNA. The answer becomes clear when we look further into the meaning and scope of the claims of the '525 patent. The language of the '525 patent and trial testimony convince us that the proper meaning and scope of the '525 claims prevent UC from prevailing in its contention that Lilly's plasmid infringes the '525 patent under the doctrine of equivalents. We explain.

In trial, Lilly established that approximately the first third of the proinsulin-encoding sequence contained in its plasmid is synthesized chemically. Lilly uses this chemically synthesized

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[5] According to the specification of the '740 patent, a plasmid is an example of a transfer vector commonly used in bacterial genetics. A vector is "a DNA molecule which contains genetic information which insures its own replication when transferred to a host microorganism strain." UC Ex. 1 at col. 4, ln. 25.

portion so that its proinsulin-encoding sequence begins precisely at the first amino acid for human proinsulin. Tr. at 1390-91. The technique of providing such a precise starting point is called tailoring. Lilly's expert Dr. Walter Gilbert[6] (Gilbert) testified that the techniques described in the '525 patent do not disclose tailoring techniques. Tr. at 1391, 1394. Gilbert further averred that he was unaware of any cDNA cloning [7] experiments using the technology revealed in the '525 patent yielding a piece of cDNA starting precisely at the beginning of the proinsulin-encoding sequence. Tr. at 1398. The evidence indicates that all cloned cDNAs during the relevant time period were either too long or too short to encode human proinsulin precisely.

Moreover, in the prosecution of another of UC's Patents -- the '740 patent, which bears a file date later than that of the '525 -- UC representatives argued to the United States Patent and Trademark Office (PTO) examiner that

prior art cloned cDNAs, such as disclosed by the cited references, have not provided defined precise starting points but have instead been either too long, comprising 5 '

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[6] Dr. Gilbert is a 1980 Nobel Laureate in chemistry and the author or co-author of some 123 articles on various phases of molecular biology.

[7] Cloning is defined as "the formation of a clone." Dorland's Medical Dictionary at 346. (27th ed. 1988). DNA cloning is defined as "in genetics, the production of many identical copies of a specific DNA fragment. "*Id.* at 346-47. Clone is defined as, *inter alia*, "a DNA population derived from a single hybrid DNA molecule (recombinant vector, *q.v.*) by replication in a eukaryotic or bacterial host cell. "*Id.* at 346.

untranslated regions,[8] or too short, being fragments of the desired sequence. No techniques for tailoring cloned cDNAs to provide a defined starting point have been disclosed in the prior art.

Lilly Ex. 3029E at A000176-77.

The cited references to which this quoted passage refers includes a paper by Ullrich and other scientists (Ullrich *et al.*) published in *Science* on June 17, 1977. The PTO examiner's citation of the Ullrich *et al.* paper is particularly relevant to this discussion because that paper provides the basic disclosure for the specification of the '525 patent. Indeed, Gilbert testified that "the '525 patent doesn't reveal any technique that is not revealed in the Ullrich publication; and therefore, provides no technique to provide a defined end." Tr. at 1394; see also tr. at 561. UC's argument during prosecution of the '740 patent, quoted above, was an effort to prevent rejection of certain claims in the '740 patent based on lack of novelty or obviousness in light of, among other references, the Ullrich *et al.* paper. Such argument is telling evidence of UC's position concerning the disclosure of the '525 patent. It is obvious that even UC believed that the '525 patent did not disclose the tailoring techniques presently in issue. Indeed, the PTO examiner's eventual decision to issue certain of the claims in the '740 patent was based on his determination that the human proinsulin-encoding sequences contained in those claims were tailored, rendering them patentable over the prior art. UC Ex. 3 at A000172, A000254.

UC's argument countering Lilly's position is unpersuasive. Trial testimony indicated that use of the cloning method

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[8] The ' in "5' " stands for prime, and the 5' region is the area upstream of (or preceding) the DNA coding for human proinsulin.

described in the '525 patent would yield molecules of a variety of lengths. Tr. at 722, 1472. From this, UC attempted to establish that within this array of molecules would be that one molecule beginning precisely at the starting point for human proinsulin. Gilbert, however, testified that although the possibility existed that one could find the molecule with the precise starting point, the possibility is rather low. Tr. at 1473. " [T]hat molecule may be there, and it, in fact, may not be there. It may be there at one part in a million or one part in a billion." Tr. at 1473. Moreover, UC's expert Dr. John Richards (Richards) testified that he was unaware of any experiments using the technology in the ' 525 patent or the *Ullrich et al.* paper that resulted in a molecule starting precisely at the beginning of the proinsulin sequence. Tr. at 724.

The Court is not convinced that a DNA sequence specifically tailored to a precise beginning infringes a patent that fortuitously carries with it an unlikely possibility that a scientist, using the methods of the patent, may locate a cDNA having a precise starting point. For these reasons and in the wake of another examination of the language of the '525 patent, we find that the '525 patent, properly interpreted, fails to provide the tailoring techniques necessary to enable one skilled in the art to prepare a coding sequence whose starting point corresponds precisely with the first amino acid for human proinsulin. Because the specification does not so provide, we find that the claims cannot be read to encompass plasmids and microorganisms containing tailored coding sequences.

Significant to our decision, we do not believe that a plasmid made by the method of the '525 patent either would perform in substantially the same way or result in the same product as would a plasmid containing a tailored coding sequence such as the one Lilly uses. Specifically, Gilbert testified that use of a sequence that was either too long or too short to encode

proinsulin precisely would not work in Lilly's system. Tr. at 1390-91. He averred that Lilly's system requires use of a plasmid that contains an insert encoding the exact amino acid sequence for human proinsulin. *Id.*

The '525 patent does not disclose such a plasmid or an equivalent thereof. Moreover, Lilly expert Robert Armitage (Armitage) testified that Lilly's plasmid makes substantial molecular departures from the natural cDNA sequence provided in the '525 patent. Tr. at 1859. The differences include, but are not limited to, the removal of the "first 100 nucleotide bases of the natural sequence and [substitution of] a synthetic sequence that has on the order of 20 changes from the natural sequence which would be the sequence represented for human cDNA had that structure actually been available and included in the '525 patent."[9] Tr. at 1859. Consequently, we find that Lilly does not infringe the subject claims of the '525 patent under the doctrine of equivalents.

B. The '740 Patent

UC alleges that Lilly's accused plasmid both literally infringes the '740 patent and infringes under the doctrine of equivalents. We will begin by addressing UC's allegations of literal infringement. UC contends that Lilly literally infringes claims five, six and eight through ten of the '740 patent.

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[9] Research leading to the application for the '525 patent was conducted in the rat. At the time the application for the '525 patent was filed, human proinsulin cDNA had not been isolated and characterized.

1. Literal Infringement

a. Claims five and six [10] Claims five and six claim:

5. A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin consisting essentially of a plus strand having the sequence:

[selected from among all possible DNA sequences encoding human proinsulin).

6. A microorganism transformed by the transfer vector of claim 4 or 5.

UC Ex. l at cols. 17-18.

Previously, UC moved the Court for summary judgment on Lilly's alleged literal infringement of claims five and six of the '740 patent. In response to UC's motion, Lilly argued that its use of a fusion protein precluded UC from succeeding with its literal infringement charge. We denied UC's motion, explaining that it was necessary for us to obtain more information before we could discharge our duty of claim interpretation.

The DNA that Lilly employs in its recombinant production of human insulin is a fusion protein consisting of three parts: a bacterial protein, a methionine residue and a semisynthetic proinsulin-encoding sequence. Lilly's DNA is referred to as a fusion protein because, in essence, the three parts are fused together in order ultimately to produce the desired proinsulin. The function of the bacterial protein preceding the methionine

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[10] We have combined consideration of claims five and six because claim six is dependent upon claim five. If claim five literally is not infringed, neither is dependent claim six.

and the proinsulin-encoding sequence is to protect the desired product from degradation. The methionine residue is inserted between the bacterial protein and the proinsulin-encoding sequence. It provides a cleavage point such that after the DNA is inserted into a plasmid, that, in turn, is inserted into a bacterium for production of the fusion protein, the bacterial portion of the fusion protein can be cleaved (or removed) from the human portion. [11]

Having now heard all the evidence, the Court again has examined the prosecution history of the '740, its specification and its claims, and has heard experts on the matter at hand. In light of this evidence, we find that Lilly's use of a fusion protein in its production of human (pro)insulin prevents Lilly from literally infringing claims five and six of UC's patent.

Several factors indicate that a fusion protein encoding for human proinsulin cannot literally infringe claim five of the '740 patent. The prosecution history illustrates that the PTO examiner believed that DNA transfer vectors containing human proinsulin fusion proteins were in the prior art.[12] We agree

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[11] At least during the relevant time period, an alternative method for producing the desired product was called direct expression. With direct expression, there was no fusion of a protective bacterial protein to the desired product. Hence, the desired product was expressed directly -- with no subsequent need for cleaving. See UC Ex. 1 at cols. 9-10 (explaining differences between two types of expression).

[12] The examiner cited Ullrich *et al.*, Villa-Komaroff *et al.*, Cohen *et al.*, and Crea *et al.* as prior art that mandated rejection of claims one through eleven. The examiner's reference to Ullrich *et al.* included two articles: "Rat Insulin Genes: Construction of Plasmids Containing the Coding Sequences," 196 *Science* 1313-19 (June 17, 1977) (authors are Ullrich, Shine, Chirgwin, Pictet, Edmund Tischer, Rutter and Goodman), see UC Ex. 98; and "The Structure and Expression of the Insulin Gene,"

(continued...)

with his assessment. The Ullrich *et al.* Science article and the Villa-Komaroff *et al.* article disclose the cloning of rat insulin cDNA. In his first rejection of the '740 patent application, the examiner stated that, in light of the prior art, it would be obvious to prepare human insulin genes rather than rat insulin genes. UC Ex. 3 at A000142.

In an attempt to overcome the examiner's initial rejection of the claims, UC argued that the prior art cited against the '740 patent application did not teach

> essential aspects of the method of preparing the claimed compounds or compositions. Furthermore, the compounds themselves have unobvious structural and functional properties not taught, suggested or predictable from the prior art.

UC Ex. 3 at A000154.

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[12](...continued)
Proceedings of the Symposium on Proinsulin, Insulin and C-Peptide, Tokushima at 20-26 (July 1978), Lilly Ex. 3180. The Villa-Komaroff *et al.* article the examiner cited was: "A Bacterial Clone Synthesizing Proinsulin," 75 *Proceedings of the Nat'l Academy of Sciences* 3727-31 (Aug. 1978) (authors are Lydia Villa-Komaroff, Argiris Efstratiadis, Stephanie Broome, Peter Lomedico, Richard Tizard, Stephen Naber, William Chick and Walter Gilbert). *See* Lilly Ex. 3182.

In his reference to Crea *et al.*, the examiner was citing "Chemical Synthesis of Genes for Human Insulin," 75 *Proceedings of the Nat'l Academy of Sciences* 5765-69 (Dec. 1978) (authors are Roberto Crea, Adam Kraszewski, Tadaaki Hirose and Keiichi Itakura). *See* Lilly Ex. 3100. The examiner's Cohen *et al.*, reference was to United States Patent Number 4,237,224, entitled "Process for Producing Biologically Functional Molecular Chimeras." The patent's application was filed on January 4, 1979, and the patent issued on December 2, 1980. The inventors are Stanley Cohen and Herbert Boyer. *See* Lilly Ex. 2260.

The PTO examiner disagreed. He first reiterated his rejection based on the Ullrich and Villa-Komaroff articles and the articles' disclosure of the cloning of rat insulin cDNA. Significantly, he continued his rejection rationale, stating that Ullrich and Villa-Komaroff "suggest that their *processes* should be applicable to the expression of any eukaryotic protein including human insulin." UC Ex. 3 at A000166 (emphasis added). The page citations the examiner provides for the Ullrich and Villa-Komaroff process references correspond to discussions in those articles concerning fusion protein processes.

For example, the examiner refers the applicant to page 3730, column two of the Villa-Komaroff *et al.* article, an article that plainly discusses the expression of a fusion product. At the examiner's pinpoint cite, the authors are discussing fusion proteins. Significantly, in column two the authors assert, "Clearly we have exploited a general method that should lead to the expression and secretion of any eukaryotic protein provided another protein, such as penicillinase, will serve as a carrier, by virtue of its leader sequence." Lilly Ex. 3182 at 3730. Indeed, Lilly's experts Dr. Robert Old (Old) and Armitage testified that the Villa-Komaroff *et al.* article describes the production of fusion protein DNA sequences. [13] Tr. at 1618-19, 1628, 1799.

In his rejection, the PTO examiner also cites to specific pages in the Ullrich *et al. Symposium* paper. On one of those pages, the authors state:

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[13] These experts also testified that the Crea *et al.*, article and Ullrich *et al.*, *Symposium* article describe the production of fusion protein DNA sequences. Tr. at 1619, 1628, 1799.

Because of the differences between eukaryotic and prokaryotic transcriptional and translational regulatory elements, it is necessary to combine the genetic information for the eukaryotic insulin gene with prokaryotic regulatory sequences, to obtain expression of insulin in bacteria. . . .

Two plasmids have been constructed, in which the insulin DNA fragment is fused to different length portions of the gene for B-galactosidase, the first gene in the lactose operon. . . .

Lilly Ex. 3180 at 24. The authors further relate that although they had no success when fusing the protein to a short segment of the B-galactosidase gene, yet the desired protein was detected wherein the rat insulin gene was fused to a longer portion of the B-galactosidase gene. *Id.* In fact, Old testified that the *Symposium* article "describes expression and attempt at expression of a short fusion and a long fusion in bacteria." Tr. at 1618. The examiner also made reference to page 26 of the article. The authors discuss the success they had in employing the longer portion of the B-galactosidase gene and suggest that "it is possible that the large bacterial portion of the fusion product protects the insulin polypeptide from cellular protease degradation." Lilly Ex. 3180 at 26.

Finally, although the PTO examiner does not cite the Crea *et al.* article in his argument pertaining to fusion processes at this point, that article also describes use of fusion proteins in the production of human insulin through chemical synthesis of the A and B insulin chains separately. Crea *et al.* fused the genes for the A and B chains of insulin to the E. coli B-galactosidase gene. *See* Lilly Ex. 3100; *see also* tr. at 1616-17.

As we stated previously, we agree with the examiner's determination that the prior art encompassed human proinsulin fusion proteins. We are even more convinced when we add to

the prior art a publication that UC failed to bring to the attention of the PTO examiner -- European Patent Application 1929 (EPA-1929).[14] Lilly Ex. 3047 at 42. In sum, the record indicates that the prior art contained a number of references to the use of fusion proteins -- not only for the production of human proinsulin, but also for the expression of any eukaryotic protein.

Our interpretation of claim five is supported by other portions of the prosecution history. Following the PTO examiner's rejection of the claims in the '740 patent application, a UC representative had a personal interview with the examiner and, subsequently, the examiner completed an interview summary record. In it, the examiner stated:

Will limit claims to DNA transfer vector containing only the tailored starting point [of] human proinsulin and preproinsulin

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[14] Claim six of EPA-1929 claims, *inter alia*, a plasmid comprising a fusion protein encoding human proinsulin, in which the bacterial portion of the fusion protein is homologous to the bacterial host into which the plasmid will be inserted and the human proinsulin portion is a polypeptide heterologous to the bacterial host. As a model, the EPA-1929 inventors used the heterologous polypeptide somatostatin, chemically synthesizing that gene. The inventors further state that their synthesizing techniques can be used to code for "virtually any known amino acid sequence." Lilly Ex. 3047 at 11. The authors of EPA-1929 specifically reference human proinsulin in the body of their publication and indisputably claim human proinsulin, as well as various other polypeptides, in claim six. Lilly Ex. 3047.

UC argues that EPA-1929 was less relevant prior art than other prior art it cited to the examiner. UC also contends that a portion of the amino acid sequence for human proinsulin was unknown prior to the application for the '740 patent. If this were so, EPA-1929's claim to human proinsulin would be invalid as nonenabling. We only need state at this point that we disagree with UC's position. These issues will be discussed, *infra*, in detail.

as for example as recited in claim 5. If so properly limited will allow since references do not show or contemplate that feature.

UC Ex. 3 at A000172.

In response to the examiner's comment, UC submitted an amendment to claim two. As originally submitted, claim two read: "A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin." UC Ex. 3 at A000036. UC's amended claim two claimed:

A DNA transfer vector comprising an *inserted cDNA having* a deoxynucleotide sequence coding for human proinsulin [.] , *the plus strand of said cDNA having a defined 5 'end, said 5 'end being the first deox y nucleotide of the sequence coding for said proinsulin.*

UC Ex. 3 at A000173-74. With this amendment, UC narrowed the focus of claim two to tailored human proinsulin cDNA. In its previous claim two language, UC had encompassed all sequences coding for human proinsulin, whether or not the nucleotide sequence mirrored that found in the natural source -- in this case, the human -- and whether or not the cDNA was tailored.

Accompanying the amendment were UC's remarks in further support of patentability. UC reasoned that the examiner fully had not considered that its invention involved more than the cloning of cDNA for human proinsulin. UC contended that the invention

also includes additional modifications of the cloned cDNA. Such modifications are termed "tailoring", since they involve a custom-designed sequence of reactions to remove specific portions of the 5 ' region of the cDNA, yielding transfer vectors

in which the human cDNA moiety has a specific defined starting point. Two such defined starting points disclosed herein include the start of the preproinsulin coding segment and the start of the proinsulin coding segment. The claims have been amended to more particularly point out and distinctly claim the invention with respect to the tailoring aspect.

The invention herein is perceived as including a novel and unobviously attainable structural feature, namely a defined starting point at the 5 ' end (relative to the plus strand of the cDNA). Such defined starting points are obtained by complex and individualized "tailoring" reactions. Such tailoring reactions are designed to specifically remove portions of the 5 ' end of the plus strand of cloned cDNA to yield a cloned cDNA having a defined 5 ' start point different from that originally cloned. . . .

UC Ex. 3 at A000175. UC did not submit an amendment for claim five -- another claim originally encompassing all DNA sequences encoding human proinsulin.

The examiner considered UC's amendment and remarks and rejected all claims. Subsequently, UC's appeal of the examiner's decision, the notice of which was lodged in May of 1982, was dismissed, apparently because UC failed to file a brief. On June 8, 1982, UC filed a continuation of the same patent application accompanied by a preliminary amendment. That preliminary amendment included, inter alia, a further amendment to claim two. This amendment changed the phrase that previously read "an inserted cDNA having" to "an inserted cDNA consisting essentially of." UC Ex. 3 at A000248. Again, UC offered no change to claim five.

Following this second proffered amendment, the examiner conducted a telephone interview with UC in which claims two

and five, among others, were discussed, as was the prior art of Ullrich *et al.*, Villa-Komaroff *et al.* and Crea *et al.* See UC Ex.3 at A000252. After the interview, the examiner completed a notice of allowance of certain claims, including claims two and five. The claims were allowed in view of the examiner's amendment to the record. The examiner's amendment encompassed not only the language change included in UC's second amendment to claim two, but also a change in the language of claim five. Originally, claim five claimed:

A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin comprising a plus strand having the sequence:

[selected from among all the possible DNA sequences coding for human proinsulin].

UC Ex. 3 at A000037. The examiner's amendment stipulated that UC change its second use of the word "comprising" in

claim five to the phrase "consisting essentially of,"[15] so that the claim now reads:

A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin consisting essentially of a plus strand having the sequence:

[selected from among all the possible DNA sequences coding for human proinsulin].

Id. at A000254. His reasons for allowing the claims to issue, as amended, were as follows:

The claims are deemed to define over the prior art for substantially the reasons advanced in the amendment filed

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[15] Some information pertaining to patent claim drafting is in order. There are three parts to a claim: the preamble, the transition and the body. The transition is the part with which we currently are concerned. Generally, there are three categories of transitions. See D. Chism, Patents, Section 8.06 [1] at 8-99. An open-ended transition is recognized by use of the term "comprising" or the phrase "which comprises."*Id.* at 8-100-8-101. A closed-ended transition employs either the phrase "consisting of" or the phrase "which consists of."*Id.* Finally, the intermediate transition, sometimes referred to as nearly closed-ended, is identified by either the phrase "consisting essentially of" or "which consists essentially of."*Id.* at 8-10-2. The intermediate transition excludes "additional, unspecified components that would affect the basic and novel characteristics of the product defined in the balance of the claim."*Id.*

We note that claim five of the '740 patent includes both the term "comprising" and the phrase "consisting essentially of." "Comprising," however, is used in claim five to qualify that which the transfer vector may contain, while the phrase "consisting essentially of" limits that which the DNA sequence coding for human proinsulin may contain. This case more narrowly focuses on the content of the DNA insert coding for human proinsulin. Hence, the more restrictive transition is applicable to the ensuing discussion.

April 5, 1982 (paper No. 19) of parent application Serial No. 075,192 and because the examiner's amendment excludes from the cDNA the presence of sequences other than proinsulin or preproinsulin.

Id. The examiner told UC that should the changes be unacceptable, UC had the option of filing an amendment pursuant to 37 C.F.R. 1.312 (Rule 312 amendment).

UC urges the Court to find that the examiner's mandated amendment and reasons therefore illustrate that he was excluding from the claims in issue only naturally occurring sequences -- an exclusion, UC argues, that does not encompass the substances preceding Lilly's proinsulin-coding sequence. UC points to the examiner's use of the acronym "cDNA" when he cited his reasons for the mandated amendment. Since cDNA refers only to the DNA sequence found in the natural source, UC contends, the examiner's exclusion only prevents the patented claims from including substances that naturally occur upstream from the proinsulin-encoding sequence.

Lilly contends, however, that the examiner's mandated amendment is proof that claim five cannot be interpreted as covering fusion proteins. Lilly first focuses on the examiner's addition of the phrase "consisting essentially of" to claim five. This phrase, Lilly argues, precludes the claims in issue from encompassing a vector with an inserted DNA sequence containing *any* elements upstream from the tailored starting point of human proinsulin. Lilly asserts that the examiner's agreement with this position is illustrated in the first interview summary record where he stated that the claims would be allowed if UC limited them to DNA transfer vectors containing "*only* the tailored starting point [of] human proinsulin and preproinsulin. . . ." UC Ex. 3 at A000172 (emphasis added). In response to UC's argument that the examiner's use of the

acronym "cDNA" indicates alliance with UC's camp, Lilly reasons that his use of the acronym was merely a misnomer. Lilly asserts that the examiner's notes from both interviews with UC must be read together in order accurately to determine the examiner's intent, and that such a reading illustrates that the examiner intended to exclude fusion proteins from claim five. An examination of the amendments to claims two and five and trial testimony, as well as our earlier perusal of the prior art, persuade us that Lilly's position is well taken. First, the examiner's initial summary record unambiguously supports Lilly's position. In that record, the examiner states that he will allow the subject claims if UC structures those claims to encompass transfer vectors containing *only* the tailored starting point of human proinsulin. In response, UC amended only claim two and did so in such a fashion that, if accepted, it undoubtedly would have encompassed human proinsulin fusion proteins. Tr. at 1797. UC's use of the phrase "an inserted cDNA *having* a deoxynucleotide sequence . . ,"*id.* (emphasis added), would have meant that UC's insert not only would have a cDNA sequence coding for human proinsulin, but also could have other unenumerated sequences -- for example, a fusion protein. Thus, in this state, claim two encompassed use of a fusion protein to produce human proinsulin via a tailored cDNA.

The examiner, however, did not accept UC's proffered amendment. When the matter came before the examiner again, UC had replaced claim two's phrase "an inserted cDNA having" with "an inserted cDNA consisting essentially of." We find that this version of the claim not only retained the claim's limitation of a tailored cDNA, but also further restricted the claim to direct expression by employing use of the nearly closed-ended phrase "consisting essentially of."

Still, UC had not amended claim five. In its unaltered state, claim five certainly would have encompassed fusion proteins. However, before the examiner would allow claim five to issue, he mandated that the limiting language be added. Thus, claim five as issued covers transfer vectors that include a DNA sequence coding for human proinsulin *consisting essentially of* any of the sequences that code for that protein. We conclude that the examiner's addition of he phrase "consisting essentially of" is additional proof that he believed human proinsulin fusion proteins were not patentable to UC. By mandating use of the limiting language, the examiner strategically excluded fusion proteins from UC's claims. We further conclude that the examiner intended to use the acronym "DNA" rather than "cDNA" in his reasons for allowing the claims finally to issue. This reading not only is consistent with the mandated claim language and the prior art, but also takes into consideration claim five's focus on the trillions of DNA sequences that are not identical to the cDNA sequence.

Furthermore, Armitage pointed out yet another excerpt from the prosecution history of the '740 patent that suggests the examiner meant "DNA" when he used the term "cDNA" in his statement of reasons for allowing the subject claims to issue. Specifically, in the examiner's statement, he said that the claims define over the prior art for the reasons advanced in UC's April 5, 1982, amendment and because his amendment -- the amendment now in issue -- excludes from the cDNA the presence of sequences other than proinsulin. UC Ex. 3 at A000254. In UC's April 5, 1982, amendment, UC contended that its claims were patentable over the prior art largely because of the tailoring aspect -- that is, the removal of specific portions of the cDNA to yield a defined starting point. UC Ex. 3 at A000174-77. If UC's argument were correct and the examiner actually meant only cDNA when he used that term, the examiner's reasons for allowance would be redundant; he

would be reasoning that the claims define over the prior art because the cDNA is tailored (as articulated in UC's April 5, 1982, amendment) and because the cDNA is tailored (as UC would have the Court interpret the examiner's reference to cDNA). We are persuaded that this was not the examiner's intent.

Finally, we turn to another portion of the prosecution history supporting our conclusion that fusion proteins literally cannot infringe claims five or six of the '740 patent. We earlier noted that in his amendment to the patent claims, the examiner informed UC that if the changes he mandated were unacceptable, UC could file a Rule 312 amendment. UC apparently was not satisfied with the examiner's amendment. On June 23, 1983, UC filed a Rule 312 amendment in an attempt, UC reasoned, "to include in each of the claims linkers, poly-G-C tails or other connectors attached to either side of each sequence in question." UC Ex. 3 at A000264. UC described the additions as "trivial." In the Rule 312 amendment, UC requested, *inter alia*, the following revisions to claims two and five:

2. (Thrice Amended) A DNA transfer vector comprising an inserted DNA comprising a cDNA consisting essentially of a deoxynucleotide sequence coding for human proinsulin, the plus strand of said cDNA having a defined 5 ' end, said 5 ' end being the first deoxynucleotide of the sequence coding for said proinsulin.

. . .

Claim 5, first three lines, should read as follows:

5. (Twice Amended) A DNA transfer vector comprising an inserted DNA comprising a plus strand [deoxynucleotide sequence] consisting essentially of the deoxynucleotide

sequence coding for human proinsulin, said sequence [consisting essentially of a plus strand] having the sequence:

UC Ex. 3 at A000263. If UC's amendment had been accepted, the claims clearly would have brought fusion proteins within their purview. The examiner, however, did not deem the additions trivial. In fact, he found that UC's proposed Rule 312 amendment raised new issues of scope and support and denied UC's request to amend. UC Ex. 3 at A000265. This denial provides yet another indication that the examiner believed that human proinsulin fusion proteins were not patentable to UC. We concur in his conclusion.

Also significant to this discussion is the divisional application UC filed October 24, 1983, stemming from the application that matured into the ' 740 patent and having the same specification. Lilly Ex. 3030 at OFW 776. Early in the prosecution of the '740 patent application, the examiner informed UC that its patent claims were directed to more than one invention and, therefore, stipulated that UC restrict its claims accordingly. Eventually, the claims directed to fusion proteins -- original claims twelve and thirteen -- were determined to be distinct claims such that they could support a separate patent. *See* UC Ex. 3 at A000134-142. UC chose to prosecute claims one to eleven -- claims twelve through twenty-one, including the fusion protein claims, were withdrawn from consideration.

Later, in the aforementioned divisional application, UC again brought the fusion protein claims to the forefront, at which time the examiner rejected them as unpatentable. In his first rejection, the examiner asserted that a combination of Ullrich *et al.*, Villa Komaroff *et al.* and Crea *et al.* rendered obvious fused proteins for human proinsulin. See Lilly Ex. 3030 at OFW 791-92. In response, UC submitted an amendment in which it cancelled claims twelve and thirteen without prejudice

and added new claims twenty-two through twenty-four.[16] In his rejection of these new fusion protein claims, the examiner found yet another reference upon which to base his rejection -- United States Patent Number 4,366,246 (the '246 patent).[17] Lilly Ex. 3030 at OFW 807. The examiner stated:

Riggs teach methods of preparing mammalian fusion proteins (human somatostatin and insulin) wherein the entire mammalian protein is fused at its C-terminus to the N-terminus of a procaryotic protein with an intermediate enzymatically cleavable segment joining the termini. . . . Further, while Riggs primarily chemically synthesizes his genes . . . prior to cloning and expression he also does embrace the use of cDNA genes resulting from reverse transcription from mRNA, and specifically those of Ullrich *et al.* It would be obvious to use the teaching of Riggs in the preparation of human proinsulin and preproinsulin as would result from the other combined

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[16] Claims twenty-two and twenty-four claimed as follows:

--22. A fusion protein comprising the complete amino acid sequence of human proinsulin as its C-terminus sequence,

a portion of a prokaryotic protein as its N-terminus sequence, and joining the C-terminus and N-terminus sequences, an intermediate segment at which the fusion protein can be cleaved enzymatically to release full- sequence proinsulin free of the N-terminus sequence.

--24. The protein of claim 22 wherein the intermediate segment is a polylysine segment, and the protein can be selectively cleaved by digestion with carboxypeptidase B or cathepsin B, to release full-sequence human proinsulin from the lysine residues and attached N-terminus sequence.--

Lilly Ex. 3030 at OFW 798-99. Claim twenty- three is not relevant to our discussion.

[17] The '246 patent is entitled "Method for Microbial Polypeptide Expression," and its inventor is Arthur Riggs. The application for the '246 patent has an application date of November 8, 1977; the patent issued on December 28, 1982.

references. Additionally it would be obvious to construct the insulin fusion proteins by conventional peptide chemistry.

Id. at OFW 807-08. Subsequently, UC abandoned its divisional application. *See* Lilly 3030 at OFW 822.

An examination of the language of claims twenty-two and twenty-four in UC's divisional application leads us to conclude that UC, itself, did not believe that it had captured human proinsulin fusion proteins in the '740 patent. Hence, UC attempted to do so in its divisional application. UC's attempt in 1986 to patent that which it now asserts is encompassed in the '740 patent lends further support to our interpretation of the claims in issue.

We find it prudent to address one last issue before concluding this literal infringement analysis. The issue involves the language of claim fourteen, which claims a specific semisynthetic sequence coding for human proinsulin. Tr. at 1655-56. Amino acid position one of that sequence is preceded by the codon for methionine. *See* UC Ex. 1 at col. 20; tr. at 1827. At trial, it was suggested that claim fourteen's inclusion of a codon for methionine evidences the PTO examiner's willingness to grant fusion proteins to UC. We believe proper interpretation of claim fourteen dispels such a suggestion.

Armitage explained that methionine is a start codon; that is, a codon that "signals the cell that it's time to start producing protein from the DNA sequence." Tr. 1827. He opined that the fact that the PTO examiner allowed UC to include this start codon in claim fourteen does not suggest that the examiner was permitting UC to claim fusion proteins. Tr. at 1827-28. The examiner, he testified, could have mandated the use of language prohibiting the use of this methionine codon, but that such mandate would have been "complete nonsense." Armitage

reasoned that no substance can be expressed via the technology in issue without a start codon. *Id.* In fact, he averred that use of a start codon is "how direct expression takes place." Tr. at 1828. We find Armitage's testimony credible, we heard nothing to contradict his statements, and, thus, we do not believe that inclusion of a start codon in claim fourteen reflects that the examiner was granting fusion proteins to UC.

Moreover, we agree with Armitage's testimony concerning example 2A of the ' 740 patent's specification. In example 2A, the inventors describe use of a fusion protein. UC Ex. 1 at cols. 12-13. Further into the patent specification, the inventors in example 3 discuss expression both as a fusion product and through direct expression. *Id.* at cols. 15-16. As Armitage testified:

Well, the prior art references that the examiner applied taught fusion proteins but not direct expression. This patent teaches both fusion protein expression and direct expression; and therefore, the examiner found what he believed to be a basis for a patentable distinction of these claims over the references that he cited.

Tr. at 1829-30. We agree. Although UC attempted to garner both fusion protein expression and direct expression, the prosecution history of the '740 patent application indicates that it was successful only in its bid for direct expression claims. We are unconvinced that the inclusion of a start codon in claim fourteen signifies that UC's claims encompass fusion proteins.

In conclusion, we believe the PTO examiner found that claim five was patentable only to the extent that it claimed vectors coding for the direct expression of human proinsulin, and we agree with his determination. As we discussed earlier, construction of a fusion protein was in the prior art, not only for

(pro)insulin, but also for other proteins. Also significant to the Court's interpretation of claim five is our belief that the amino acid sequence for human proinsulin was in the prior art.[18] Consequently, the transfer vector patented in claim five is that which provides for direct expression of human proinsulin. Fusion proteins are excluded. For these reasons, Lilly's accused plasmid does not literally infringe claims five and six of UC's '740 patent.

b. Claims eight, nine and ten

UC also accuses Lilly of literal infringement of claims eight through ten of the '740 patent. In those claims, the inventors claim:

8. The plasmid pcHP-1.

9. A microorganism transformed by the plasmid of claim 7 or 8.

10. A microorganism as in claim 9 wherein the organism is *Escherichia coli.*

Claims nine and ten, to the extent they are involved in this action, are dependent on claim eight. As stated previously, the determination we reach regarding the independent claim applies with equal force to its dependent claims.

In the specification of the '740 patent, the inventors state that " [a] plasmid transfer vector comprising pBR322 with an inserted proinsulin coding sequence is designated pcHP-1." UC Ex. 1, col. 12 at lns. 49-51. In an effort to establish Lilly's

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[18] We discuss this issue in detail at pages 46 through 65.

infringement of claim eight, UC questioned expert Richards. Richards testified that he believes Lilly's plasmid infringes because it contains a pBR322 element with an inserted proinsulinencoding sequence. Tr. at 640-41.

Richards further testified that under his interpretation of claim eight, a plasmid already described in the prior art would fall within the scope of claim eight if a synthetic human proinsulin DNA sequence were substituted for the somatostatin DNA sequence actually described in that prior art. Tr. at 688-90. Significantly, the prior art to which Richards referred was EPA-1929, the published patent application earlier discussed in this Opinion, which, in claim six, claims a plasmid encoding a fusion protein for human proinsulin. Tr. at 687-691. If the Court were to interpret and validate claim eight as broadly as UC suggests, claim eight would encompass the subject matter of claim six of EPA-1929, which is prior art to the '740 patent.

The Court, however, does not interpret claim eight nearly so broadly as UC urges. To interpret claim eight as UC suggests would be to broaden the scope of the '740 patent far beyond that anticipated by the examiner as evidenced by the prosecution history. Indeed, UC's interpretation would give UC in claim eight sequences that the examiner clearly refused to give it in claims two and five. We conclude that claim eight, properly interpreted, requires that the proinsulin-encoding sequence inserted into the claimed plasmid, like those sequences in claims two and five, be a sequence coding for direct expression, i.e., not a fusion protein. Not only is this interpretation consistent with the prosecution history of the patent application, but also it is consistent with preexisting claim six of EPA-1929. In summary, we find that Lilly's plasmid does not literally infringe claims eight, nine and ten of UC's '740 patent. We now turn to the issue of infringement under the doctrine of equivalents.

2. Infringement Under the Doctrine of Equivalents

Our analysis does not end with a determination that there is no literal infringement of the subject claims. UC also alleges that Lilly's accused plasmid infringes claims two, three, thirteen and fourteen under the doctrine of equivalents.[19] Thus, we must determine if Lilly has made nothing more than "unimportant and insubstantial changes and substitutions in the patent which, though adding nothing, would be enough to take the copied matter outside the claim. "*Graver Tank Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 607 [85 USPQ 328] (1950). We begin with an analysis of claim two of the '740 patent.[20]

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[19] Claims two, three, thirteen and fourteen of the '740 patent read:

2. A DNA transfer vector comprising an inserted cDNA consisting essentially of a deoxynucleotide sequence coding for human proinsulin, the plus strand of said cDNA having a defined 5 ' end, said 5 ' end being the first deoxynucleotide of the sequence coding for said proinsulin.

3. A microorganisms [sic] transformed by the transfer vector of claim 1 or 2. . . . 13. The DNA transfer vector of claim 5 wherein:

[DNA sequence encoding the natural sequence (cDNA) for human proinsulin].

14. The DNA transfer vector of claim 5 wherein the codon for amino acid position one is preceded by 5 '-ATG and

[DNA sequence encoding for a semisynthetic human proinsulin protein].

UC Ex. 1 at cols. 16-20.

[20] Claim three is dependent on claim two, and claim thirteen describes a transfer vector containing the same sequence for human proinsulin as found in claim two. Thus, if claim two is not infringed under the doctrine of equivalents, neither is claim three nor claim thirteen.

UC's expert Richards testified that Lilly's plasmid infringes claim two of the '740 patent under the doctrine of equivalents. Tr. at 633. Richards stated that the human proinsulin encoding DNA sequence Lilly uses in its plasmid is not an identical copy of the cDNA. "There are some nucleotide changes," he averred. "But," he added, "in terms of function, they're insubstantial." Tr. at 634. Richards also testified that Lilly's plasmid -- like the transfer vector described in claim two of the '740 patent -- begins precisely at the first deoxynucleotide of the sequence coding for human proinsulin. Tr. at 635.

On cross examination, Richards stated that he could not remember the number of differences in nucleotides when comparing claims two and thirteen of the ' 740 patent to Lilly's accused plasmid. Tr. at 719. He opined that the differences were inconsequential because, in spite of the differences, the semisynthetic DNA sequence Lilly uses in its plasmid encodes human proinsulin. Tr. at 719.

The Court, however, is not so quick to disregard the differences. A determination of infringement by equivalence, even if we were to consider the facts of the case under the function-way-result test alone, requires more than consideration of the result -- in this case, human proinsulin. Rather, it also requires a comparison of function and way. Moreover, according to the Federal Circuit's decision in *Hilton Davis*, consideration of evidence of function- way-result may not be sufficient in every case. Specifically, a court must consider all the evidence relevant to the substantiality of the differences between the accused and patented products.

Even more important to the instant discussion is the proper scope of the subject claims. An examination of the language of claim two and thirteen, as well as the expert testimony at trial, establishes that claims two and thirteen are directed to the

cDNA sequence. Specifically, the transfer vector that is claimed therein only encompasses the sequence of bases coding for proinsulin found in the human source.

According to Lilly's expert witness Old, there are twenty-four differences in the proinsulin nucleotide sequence between Lilly's plasmid construction and the cDNA claimed in claims two and thirteen of the '740 patent. Tr. at 1645; *see also* Lilly Ex. 4038 (asserting that there are 23 differences from the natural sequence). These differences convert Lilly's plasmid into one containing a DNA sequence that more nearly resembles a sequence described in UC's claim five -- the claim that encompasses all the possible DNA sequences for human proinsulin -- rather than the cDNA sequence described in claim two. Significantly, we earlier stated that the PTO examiner limited the scope of UC's generic claim five to direct expression, i.e., expression of proinsulin without use of a fusion protein, and we agreed with the examiner's limitation. [21]

The Court is persuaded that it would be improper to broaden the scope of claims two, three and thirteen to give to UC that which the PTO examiner found unpatentable in the context of claim five. Hence, we find that Lilly's plasmid -- a plasmid that does not consist of the cDNA for human proinsulin -- does not infringe claim two, three or thirteen of the '740 patent. Furthermore, since Lilly's plasmid coding for human proinsulin utilizes the fusion protein concept, it cannot infringe claim five of the '740 patent.

Not only does claim thirteen's DNA sequence mirror that found in claim two, but also claim thirteen claims "the DNA

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[21] The reason for this limitation is discussed in more detail in this Opinion in the preceding section regarding literal infringement and the following section concerning validity.

transfer vector of claim 5. . . ." The language of claim fourteen does likewise. Such language renders claims thirteen and fourteen dependent on claim five. Tr. at 1827. We already have found that claim five is limited to direct expression and believe that claims thirteen and fourteen also properly are limited to direct expression. Hence, we reject UC's doctrine of equivalents argument.

II. Invalidity

Lilly asserts that certain claims, both in the '525 patent and in the '740 patent, are invalid. A patent is presumed valid, and the burden of establishing invalidity is on the challenger. See 35 U.S.C. Section 282; see also *American Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1358 [220 USPQ 763] (Fed. Cir. 1984). Furthermore, a court must be persuaded by clear and convincing evidence that the patent in issue is invalid. *American Hoist & Derrick Co.*, 725 F.2d at 1360. In the instant case, we first turn to address Lilly's contention of invalidity in the context of the '525 patent.

A. The '525 Patent -- Written Description Requirement

Lilly asserts that the '525 patent's claims to natural human proinsulin DNA are invalid under the first paragraph of 35 U.S.C. Section 112 because the inventors failed to provide the requisite written description of the claimed subject matter.[22] UC counters that the '525 patent sufficiently describes that which is claimed. UC states that the inventors of the '525 patent reduced to practice the rat insulin gene. According to UC, this

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[22] Lilly previously argued the inadequacy of UC's written description in a summary judgment motion. The Court denied that motion, reasoning that further development of the record should precede a determination of the issue.

reduction to practice entitled the inventors also to claim the genera of vertebrates and mammals of claims one, two, four, six and seven[23] -- genera of which the rat is a member. Additionally, UC contends, the inventors' accomplishment with rat cDNA, in conjunction with the method the '525 taught for isolating the insulin gene, permitted the inventors to capture the proinsulin cDNA of the human species as claimed in claim five.[24] UC adds that the isolation method taught in the ' 525 patent was that method it subsequently used actually to isolate the human proinsulin cDNA.

The statutory language in issue stipulates that

[t]he specification shall contain a written description of the invention, and of the manner and process of making and using

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[23] These claims in the '525 patent read:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

2. A recombinant procaryotic microorganism modified to contain a nucleotide sequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin. . . . 4. A microorganism according to claim 2 wherein the vertebrate is a mammal. . . . 6. A plasmid according to claim 2 comprising a plasmid containing at least one genetic determinant of col E1.

7. A microorganism according to claim 2 comprising a strain of *Escherichia coli.*

[24] Claims five of the '525 patent claims:

5. A microorganism according to claim 2 wherein the vertebrate is a human.

it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. . . .

35 U.S.C. Section 112.

The legal standard for sufficiency of a patent's written description is whether that description " '. . . reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter.' "*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 [19 USPQ2d 1111] (Fed. Cir. 1991) (quoting *Ralston Purina Co. v. Far -Mar-Co., Inc.*, 772 F.2d 1570, 1575 [227 USPQ 177] (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375 [217 USPQ 1089] (Fed. Cir. 1983); *Fiers v. Revel*, 984 F.2d 1164, 1170 [25 USPQ2d 1601] (Fed. Cir. 1993) (citation omitted). Whether a patent's specification contains a disclosure that satisfies 35 U.S.C. Section 112 Para. 1 is a question of law; compliance with the written description aspect of that requirement is a question of fact. *Utter v. Hiraga*, 845 F.2d 993, 998 [6 USPQ2d 1709] (Fed. Cir. 1988) (citations omitted).

In the instant case, Lilly contends that its position is supported by *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200 [18 USPQ2d 1016] (Fed. Cir. 1991), and *Fiers v. Revel*, 984 F.2d 1164 [25 USPQ2d 1601] (Fed. Cir. 1993). In Amgen, the Federal Circuit held that

when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.

Amgen, 927 F.2d at 1206. Although Amgen dealt with the issue of conception, [25] its application to this case is clear. If an inventor has not achieved conception of an invention, he would be unable adequately to describe the invention in a fashion that satisfies 35 U.S.C. Section 112 Para. 1. In fact, the Fiers court stated:

> . . . If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived.

Fiers, 984 F.2d at 1171. Also in *Fiers*, the court explained that

> [a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. . . . A bare reference to a DNA with a statement that it can be obtained by reverse transcript ion is not a description; it does not indicate that [the patent applicant] was in possession of the DNA.

Fiers, 984 F.2d at 1170-71.

Although *Amgen* and *Fiers* provide guidance for our decision today, yet they do not furnish us with a definitive answer.

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[25] "Conception is the 'formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.' "*Amgen*, 927 F.2d at 1206 (quoting *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 [231 USPQ 81] (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987)) (further citations omitted). "Conception requires both the idea of the invention's structure and possession of an operative method of making it. "*Amgen*, 927 F.2d at 1206 (citation omitted).

Unlike the inventors in *Fiers* and *Amgen*, the inventors on the '525 patent actually had isolated and characterized a cDNA gene for insulin -- i.e., rat insulin. We must decide whether the isolation and characterization of one species allows the inventor to claim the genera in which that species is a member, as well as other species from those genera. We think that it does not.

In examples one through five of the '525 patent's specification, the inventors describe the extraction and isolation of rat insulin mRNA; the synthesis and characterization of double stranded cDNA containing the rat insulin sequence; the ligation of linkers to that double stranded cDNA; the formation of a recombinant plasmid and its characterization after replication; and further purification and sequence analysis. While prophetic example six suggests use of the procedures outlined in examples one through four within the context of human insulin, the specification provides no description of the "reverse transcript of an mRNA" for human insulin. The inventors could not provide a description of human insulin cDNA because they were not then in possession of that DNA. The '525 patent application has a file date of May 27, 1977, and the application was expanded on April 19, 1978, to add example six, relating to the potential isolation of human insulin DNA. However, it was not until nearly two years after the original application for the '525 was filed that UC inventors actually isolated and characterized human insulin cDNA.

At trial, Old opined that there are tens of thousands of members in the vertebrate genera. Tr. at 1390. The human, of course, is one species within that genera. Old testified that members of the vertebrate species do not have identical genes encoding insulin. *Id.* The human insulin cDNA, for example,

differs from the rat insulin cDNA by four codons.[26] Tr. at 1841. Gilbert testified that it is impossible to use the rat insulin cDNA sequence to determine the human insulin cDNA sequence. Tr. at 1390. UC, itself, argued in the prosecution of the '740 patent that the differences in the nucleotide sequence were of major significance, and that such differences should render the human insulin cDNA patentable over the prior art -- prior art that included the '525 patent. UC Ex. 3 at A000160-61.

The PTO examiner disagreed; indeed, he already had permitted the inventors of the '525 patent to claim human insulin cDNA. We believe, however, that Federal Circuit cases decided after the examiner's consideration of the claims in issue reveal that the examiner erred when he determined that human insulin cDNA was patentable before it actually had been isolated and characterized. The Federal Circuit's holding that an adequate written description of a DNA requires a "precise definition" leads us to conclude that the '525 patent's specification neither enables the patent's claims to all vertebrates and mammals, nor enables the claim targeting the human species. We are persuaded that the isolation and characterization of the proinsulin cDNA from one member of a genus is not sufficient to support claims to the insulin cDNA of thousands and thousands of other species from that genus. Consequently, we hold that the specification of the '525 patent adequately describes only the rat insulin cDNA; the inventors'

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[26] A codon consists of three nucleotides. A nucleotide consists of a base chemical that is linked to a 5-carbon sugar that has a phosphate group attached. See *In re O'Farrell*, 853 F.2d at 896.

claims to the genera of vertebrates and mammals and to the human species are invalid. [27]

B. The '740 Patent -- Anticipation and Enablement [28]

Preliminarily, we note that our earlier determination that claims five, six and eight through ten encompass only direct expression of human proinsulin distinguishes those claims from the prior art in issue, i.e., EPA-1929, such that EPA-1929 is not an anticipatory reference to the '740. Nevertheless, our previous interpretation of the claims in issue was based, in part, on our conclusion that the amino acid sequence for human proinsulin

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[27] Ironically, the PTO examiner did not permit UC to claim the untailored cDNA For human proinsulin in UC's later prosecution of the '740 patent, even though UC scientists actually had isolated and characterized that structure prior to filing that patent application. The examiner's rejection was based in part on the Ullrich *et al. Science* article, which formed the basis for the '525 patent. Our present determination that UC had not described adequately human proinsulin cDNA in the '525 specification indicates that the human proinsulin cDNA in its untailored state likely would have been patentable to UC over the Ullrich *et al.*, reference. Even if UC had garnered the untailored cDNA sequence for human proinsulin in its prosecution of the '740 patent, however, the result in this Opinion nevertheless would remain unchanged because, as we stated *supra*, (1) Lilly does not use the cDNA sequence in its manufacture of human (pro) insulin; and (2) Lilly uses a fusion protein in its manufacture of human (pro) insulin rather than a sequence coding for direct expression.

[28] This is not the first time that the issue of anticipation has been before this Court. Previously, Lilly moved for summary judgment of claims five and six of the '740 patent, arguing that the amino acid sequence for human proinsulin was within the common knowledge of technologists in the field before the date of the application for the '740 patent. Genuine issues of material fact dictated a denial of Lilly's motion.

existed in the art before the file date of the '740 application. Moreover, UC steadfastly contends that the subject claims of the '740 patent encompass human proinsulin fusion proteins. Hence, we believe a discussion of the invalidity and enablement issues is necessary.

Lilly argues that EPA-1929 renders claims five, six and eight through ten of the '740 patent invalid under the doctrine of anticipation, pursuant to 35 U.S.C. Section 102(a).[29] UC counters that EPA-1929 cannot be an anticipatory reference because it does not meet the requirements for such. Specifically, a claim is anticipated only if all the elements and limitations of that claim are found within a single prior art reference. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 [18 USPQ2d 1001] (Fed. Cir. 1991) (citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 619 [225 USPQ 634] (Fed. Cir.), *cert. dismissed*, 474 U.S. 976 (1985)). No difference may exist between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention. *Id.* UC asserts that EPA-1929 did not include the amino acid sequence for human proinsulin, and that such exclusion requires use of a second reference -- a use that, according to UC, prevents the instant scenario from being considered under the doctrine of anticipation.

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[29] As stipulated in 35 U.S.C. Section 102,

> [a] person shall be entitled to a patent unless--
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, ...

Lilly counters that in some instances extrinsic evidence is admissible to explain the disclosure of a reference. "This modest flexibility in the rule that anticipation requires every element of the claims to appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 [20 USPQ2d 1746] (Fed. Cir. 1991). The extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill."*Id.* at 1268.

Lilly contends that the amino acid sequence for human proinsulin was a sequence well known by those in the field of molecular biology. Consequently, Lilly posits, failure to include the sequence in EPA-1929 does not prevent that publication from anticipating certain claims of the '740 patent. Lilly also frames this issue in the context of enablement. Specifically, Lilly argues, claim six of EPA-1929 explicitly described the subject matter of the claims in issue; claim six of EPA-1929 was enabling; and, thus, EPA-1929 anticipated the subject claims of the '740 patent.[30]

Anticipation is a question of fact. *Scripps Clinic & Research Found.*, 927 F.2d at 1576. Enablement is a mixed question of law and fact, both in the context of whether a specification sufficiently enables a claim under 35 U.S.C. Section 112 and in the context of whether a prior art reference is enabling of the features for which it has been cited. *In re Epstein*, 32 F.3d

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[30] EPA-1929 bears a publication date of May 16, 1979. The application for the '740 patent has a file date of September 12, 1979. Hence, EPA-1929 is prior art to the '740 patent.

1559, 1568 [31 USPQ2d 1817] (Fed. Cir. 1994) (citing *In re Sasse*, 629 F.2d 675, 681 [207 USPQ 107] (C.C.P.A. 1980)). In order to conclude that EPA-1929 is enabling, the Court must determine that the amino acid sequence for human proinsulin, a sequence not disclosed in that prior work but essential to it, commonly was known by those skilled in the art -- that is, that the prior art did not lack an enabling disclosure. See *In re Epstein*, 32 F.3d at 1568. This same determination is necessary in order for the Court to conclude that EPA-1929 is an anticipatory reference to the '740 patent because a reference cannot anticipate that which it does not enable. See *In re Paulsen*, 30 F.3d 1475, 1480 [31 USPQ2d 1671] (Fed. Cir. 1994) (holding that prior art sufficiently was enabling to serve as an anticipatory reference).

Our first determination in this arena requires that we assume the amino acid sequence for human proinsulin was known during the relevant time period. UC contends that, even under this assumption, anticipation is an improper legal theory for consideration of the present facts because, when practicing the invention of EPA-1929, those skilled in the art necessarily had to refer to a second source in order to ascertain the desired amino acid sequence. Fundamentally, UC argues that because those skilled in the art had not committed to memory the sequence for human proinsulin, Lilly's anticipation contention is misplaced.

We are unpersuaded that individuals skilled in the art must commit complex sequences to memory in order for those sequences to qualify as information within their common knowledge. We believe that once an amino acid sequence, such as that for proinsulin, finally is determined and widely is reported within the literature of the discipline, that sequence is within the experts' common knowledge, despite the fact that the experts have not memorized the formula. In the instant case, the

sequence was reported not only in the *Atlas of Protein Sequence and Structure (Atlas)*, a reference book whose name is indicative of its contents, but also was reported in other literature in the discipline.[31]

Consequently, still operating under the assumption that the human proinsulin amino acid sequence reported was correct, the mere fact that an expert had to refer to a second source in order to obtain the specific sequence does not preclude an anticipation argument in the context of a prior art reference. We believe the modest flexibility in the rule governing anticipation is designed for just such situations. For our next analysis, we remove the presumption we previously employed and consider if the correct amino acid sequence for human proinsulin actually was in the art prior to the time EPA- 1929 was published.

Four months passed between the publication date of EPA-1929 -- which is May 16, 1979 -- and the file date of the application for the '740 patent -- which is September 12, 1979. Lilly argues that the human proinsulin amino acid sequence was known before the earlier of the two dates; UC contends that the sequence was not known until the later date, at which time inventors of the '740 patent actually isolated and characterized the human source DNA that codes for proinsulin.

Human proinsulin consists of 86 amino acids and contains three distinct segments -- the B-chain, the C-peptide and the A-chain. The C-peptide is located between the B- and A-chains

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[31] The following exhibits, the dates of which predate the application for the '740 patent, included the amino acid sequence for human proinsulin: Lilly Ex. 3118 at 1384; Lilly Ex. 3124 at 326; Lilly Ex. 3130 at 127; and Lilly Ex. 3131 at 151.

and serves to connect them. [32] During the process in which human proinsulin is converted into human insulin, the C-peptide is liberated at two cleavage sites, leaving only the A- and B-chains of human insulin.

The parties' disagreement about the human proinsulin amino acid sequence arises over the aforementioned cleavage sites (or dibasic amino acid residues). These cleavage sites are (1) the two amino acids that link the C-peptide to the B-chain of the proinsulin molecule; and (2) the two amino acids that link the C-peptide to the A-chain of that molecule. See UC Post-trial Br. at 37. Between the C-peptide and the B-chain, the amino acids are two arginines; between the C-peptide and the A-chain, the amino acids are one lysine and one arginine, in that order. Lilly contends that both the composition and order of these four residues were in the art at the time EPA-1929 was published. In contrast, UC argues that although the composition of those residues was known, yet the order in which they appeared in the proinsulin chain was not known. Consequently, we must determine the status of the knowledge regarding these dibasic amino acid residues in 1979.[33]

The human proinsulin amino acid sequence first was reported in a 1971 article entitled "Studies on Human Proinsulin: Isolation and Amino Acid Sequence of the Human Pancreatic C-Peptide" (the Oyer *et al.* article), [34] based on a study in which

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[32] According to Lilly, the C-peptide functions to bring the A-chain and the B-chain in close proximity so that they will interact to form correct disulfide bonds.

[33] EPA-1929 actually was filed November 6, 1978.

[34] The authors of the article are Philip E. Oyer, Sooja Cho, James D. Peterson and Donald F. Steiner, of the University of Chicago,

(continued...)

scientists examined the C-peptide region of human proinsulin. UC Ex. 43. The sequence identified in the Oyer *et al.* article later was catalogued in the *Atlas*, appearing in the 1972 *Atlas* and in its 1976 and 1978 supplements.

UC contends that although these publications reported the correct amino acid sequence for human proinsulin, yet the sequences were not reported with certainty. For example, UC focuses on the Oyer *et al.* article and the authors' use of such phrases as "*proposed* partial amino acid sequence of human proinsulin" and "the *probable* locations of the four additional basic residues present in human proinsulin." Lilly Ex. 3118 at 1384. Moreover, UC asserts that recitation of the proinsulin amino acid sequence in the *Atlas* and its supplements provides no more certainty than the Oyer *et al.* article. Specifically, UC notes that the dibasic residues are enclosed in special punctuation indicating that those residues only have been determined with 90 percent confidence.

In large part, the qualifying statements accompanying the published human proinsulin amino acid sequence persuaded this Court to deny Lilly's earlier motion for partial summary judgment that claims five and six of the ' 740 patent are invalid under the doctrine of anticipation. We now are convinced, however, in light of the additional evidence presented at trial, that these qualifying statements do not illustrate that the amino acid sequence for human proinsulin commonly was not known by those skilled in the art by early 1979. To the contrary, we find that it was known at least as early as 1971.

We begin our analysis with a survey of the literature and the results of research in existence prior to May of 1979. Lilly

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[34](...continued)
Department of Biochemistry.

expert Dr. Donald Steiner (Steiner) testified that during the 1968 time frame, he and co-workers determined that the dibasic amino acid residues in bovine (cow) proinsulin linking the B-chain and the C-peptide were two arginines and that the dibasic amino acid residues linking the C-peptide and the A-chain were one arginine and one lysine. Tr. at 1497-99. Steiner also averred that during the same time period, Dr. Ronald Chance (Chance), a Lilly researcher, was investigating the porcine (pig) proinsulin structure. Tr. at 1497-1498. Steiner stated that Chance established that the dibasic amino acid residues in porcine were the same as those in bovine. Tr. at 1501-02.

The identity in structure of the dibasic amino acid residues in these two mammals was no surprise to scientists, according to Steiner. Specifically, Steiner explained that these residues have a very significant function in nature -- that of providing a cleavage site for enzyme removal of the residues and the connecting C-peptide from the A- and B-chains of insulin. Tr. at 1503- 05. Because these residues play a vital role in the conversion of proinsulin to insulin, Steiner stated, its structure is highly conserved "in proinsulins across the mammalian species for sure, and probably in even much more primitive species as well." Tr. at 1503-05.

Gilbert further described the high conservation of the dibasic amino acid residues in proinsulin across the mammalian species. Gilbert first noted that the evolutionary analysis involved in the discussion of conservation of residues was in existence during the relevant time period in this case. Tr. at 1412. When asked why one would expect to find the same amino acids in the dibasic residues of all mammals, Gilbert responded:

Because [that] part of the molecule has an essential function; and therefore, a mutation which changes the amino acid tends to inactivate the molecule. Part of the molecule that doesn't have an essential function, which is sort of waving in the wind over here, when you change that amino acid, it doesn't matter. But if I've got to do something very special with that piece of the molecule and I try to change it, then I'm in trouble.

Tr. at 1414. *See also* tr. at 708 (wherein Richards, UC's expert, testified that the dibasic residues have a critical function in human proinsulin).

Gilbert explained that the evidence available before 1977 indicated that the ancestral protein for proinsulin had dibasic residues consisting of (1) two arginines between the B-chain and the C-peptide, and (2) a lysine and an arginine between the C-peptide and the A-chain. Gilbert testified that up to 1977, one might have argued that a mutation could have occurred, resulting in the human residues differing from those in the ancestral protein. Gilbert first opined that such mutation would have been extremely unlikely. Tr. at 1414-15. Second, he stated that evidence becoming available in 1977 and 1978 further strengthened the finding that the dibasic amino acid residues were highly conserved among mammals. Two experiments in the rat, another mammalian species, concluded that the residues were the same as they were for the cow and pig -- (1) two arginines and (2) one lysine and one arginine. See, e.g., Lilly Ex. 3761. Gilbert focused on the rat experiment conducted by UC scientists in his testimony. [35]

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[35] The results of this experiment formed the basis for UC's '525 patent.

Gilbert explained that this rat experiment revealed information concerning the make- up of the actual ancestral codons. [36] Tr. at 1416. According to Gilbert, this revelation was significant. Specifically, there are two sets of bases that encode the amino acid lysine; and there are six sets of bases that encode the amino acid arginine. *See* Lilly Ex. 3766. Some of the sets of bases that encode arginine would require fewer base mutations than other codons in order to change the arginine into a lysine.[37] Tr. at 1417. In the rat experiments, it was determined that the codons encoding the arginine residues were from among those sets of bases requiring two or more mutations in order to change a arginine into a lysine, making it extremely unlikely that such change would have occurred. Tr. at 1418. Gilbert testified that the likelihood of a single mutation occurring is approximately a one percent chance in every million years. Tr. at 1417. He further stated that " [t]o get two changes is then essentially the product of two, one percent chances every million years. . . [I]t's much less likely." Tr. at 1417-18. Gilbert said that the rat experiment illustrated that it was "essentially impossible" that in the dibasic residues an arginine could have changed to a lysine or that a lysine could have changed to an arginine.[38] Tr. at 1418.

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[36] Gilbert is referring to the nucleotide sequence in the natural source, rather than the amino acid sequence for which the nucleotide sequence codes.

[37] The greater the likelihood of such a change occurring, the lesser the likelihood that the amino acid sequence for human proinsulin was known at the time in question.

[38] UC's expert Richards testified that a mutation has been reported in the literature. That mutation was a single point mutation in one of the arginines in the dog. We note, however, that this single point mutation, which did not change the amino acid for which the codon codes, is the only species of mammal in which there has been any mutation spanning

(continued...)

[A]nybody who knew enough molecular biology to discuss sequences [at the time period in issue] and knew enough evolution to read the Dayhoff *Atlas* would have been quite sure that the sequence was correct as given for the . . . dibasic amino acids.

Tr. at 1418-19.

The Court finds this evidence highly persuasive. The testimony indicates that by 1971, experts in the field had no reason to doubt not only the composition of the dibasic amino acid residues in human proinsulin, but also the order of those residues. Indeed, Steiner and Richards both testified that they were unaware of any publication subsequent to the 1971 Oyer *et al.* article proposing a different structure for human proinsulin. Tr. at 707, 1532. Moreover, Steiner averred that had he believed in 1971 any question existed concerning the order of the dibasic residues, he then could have sequenced these residues by a direct method.[39] Tr. at 1532-34. Steiner said that the supply of human proinsulin was very limited at the time and, thus, was used to identify those parts of the sequence that were not conserved. Tr. at 1533-34.

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[38](...continued)
the 80 million years of mammalian history. Tr. at 2035-36.

[39] The amino acid sequence of human proinsulin reported in the Oyer *et al.* article was based on a combination of direct and indirect evidence. The C-peptide was determined via direct evidence from Edman degradation analysis. The dibasic residues, located at the ends of the C-peptide, were determined via indirect evidence. This indirect evidence included (1) compositional studies of intact human proinsulin establishing that these residues consisted of three arginine amino acids and one lysine amino acid, and (2) the sequencing evidence from other mammalian species, in conjunction with knowledge of the high conservation of the dibasic residues among mammalian species.

Other evidence suggests that even UC researchers, themselves, believed that the amino acid sequence for human proinsulin already existed in the art. The June 1977 *Science* article,[40] authored by UC's Ullrich, Shine, Chirgwin, Pictet, Edmund Tischer, Rutter and Goodman, provides one example. In that article, the researchers, *inter alia*, describe the nucleotide sequence of the cloned DNA of rat proinsulin. The authors stated:

> Previous data did not provide assignments for the basic arginine or lysine residues connecting the B-C-A peptides, although they had been inferred by analogy with the bovine, porcine, and *human proinsulin* sequences.

UC Ex. 98 at 1316. This passage reflects that the UC researchers believed that the dibasic residues in human proinsulin had been determined. Apparently, they were certain enough about the order of those residues to use them as a point of reference for the consideration of the proinsulin sequence of another mammalian species -- the rat.

Additionally, the specification of the '740 patent itself indicates that UC researchers believed that the amino acid sequence for human proinsulin already existed in the art. In the background of the invention, the inventors state that " [t]he amino acid sequence for human proinsulin, determined by conventional techniques, is given in Table 1." UC Ex. 1 at col. 1. The inventors explain that in Table 1, the C-peptide is amino acids 31-65, meaning that their description of the C-peptide includes the dibasic amino acid residues flanking each end of

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[40] This paper is entitled "Rat Insulin Genes: Construction of Plasmids Containing the Coding Sequences" and, as we stated earlier in this Opinion, provides the basic disclosure found in the '525 patent.

the C-peptide.[41] Table 1 lists these residues as arginine-arginine and lysine-arginine. *Id.* When co-inventor Bell was questioned at trial, the following colloquy ensued:

Q. Isn't it true that in your deposition when you were confronted with the text of your patent application, stating that the amino acid sequence determined by conventional techniques was described in figure 1 of your application, you stated, "I suspect we overlooked those details about the basic amino acids." Is that right?

A. You know, I can't tell you what I think at the time I read this paper. Obviously we had determined the sequence of human insulin cDNA and we wanted to have this information in print as rapidly as possible. It was being submitted as a letter to Nature where there's a limitation on words. And so we didn't include things that perhaps we should have or could have.

Q. I'd like to hand you a copy of your deposition transcript and ask you to turn to page 70. Starting at line 18, my question will be did you give the following answers to the following questions:

"Question: Would you read the text of your application in column 1 starting at line, it looks like about 487, do you see there where it says the amino acid sequence for human proinsulin determined by conventional techniques is given in table 1; do you see that?

"Answer: Yes.

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[41] It appears that some scientists included the dibasic residues with the C-peptide, while others considered the dibasic residues as separate from the C-peptide. The text of the '740 patent illustrates that the UC scientists included the dibasic residues within the C-peptide.

[Question:] "Do you have any reason to believe it was untrue when you signed it in 1979?

"Answer: I suspect we overlooked those details about the basic amino acids."

Did you give that testimony, Dr. Bell?

A. I signed this, didn't I?

Tr. at 1100-01.

Moreover, in example one of the specification, the inventors assert:

The primary structure of human proinsulin determined in this manner [that is, determined by nucleotide sequencing] agrees precisely with that obtained by previous amino acid sequencing experiments. (Dayhoff, M.D., Atlas of Protein Sequence and Structure, 5, Supp. 2, pp. 127-130 (1976) and Suppl. 3, pp. 150- 151 (1978).

UC Ex. 1 at col. 12. This language does not support UC's assertion that its inventors were claiming as a part of their invention the characterization of the amino acid sequence for human proinsulin. Rather, the inventors appear only to reaffirm that which already was reported in the literature. In light of not only the specification's lack of assertion of discovery concerning the amino acid sequence of human proinsulin, but also its language directly contradicting UC's current contention of discovery, we are clearly convinced that even UC believed that the amino acid sequence was in the art as early as 1977.

Finally, communications between UC representatives after the '740 patent issued further convince the Court that the '740

patent inventors did not consider themselves the discoverers of the amino acid sequence for human proinsulin in 1979 when they submitted the application for the '740 patent to the PTO. In October of 1985, a Lilly representative conveyed to a UC representative certain scope and validity concerns regarding claim five of the '740 patent in light of the published amino acid sequence of human proinsulin. *See* Lilly Ex. 3501.

On November 5, 1985, Marilyn Ziemer (Ziemer), UC's licensing associate, received a letter from Dr. Kate Murashige (Murashige), UC's outside patent counsel at that time. In this letter, Murashige questioned Ziemer about whether the amino acid sequences for human preproinsulin and proinsulin were known before the application for the '740 patent. UC Ex. 328. Ziemer received Murashige's letter on November 8, 1985. On that same day, Ziemer called Rutter, one of the four inventors named on the '740 patent. Although at her deposition on April 22, 1994, Ziemer[42] then could not recall her conversation with Rutter, yet she confirmed that a November 8, 1985, memorandum to the file was a document authored by her in which she recorded the subject conversation. Ziemer read what she had written in her memorandum to the file:

A. "Sequence of Proinsulin C-peptide[43] was known at the time of cloning. Only the pre sequence was not known."

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[42] Ziemer had become Ziemer Hartig by the time her deposition in this action was taken.

[43] Significantly, as we earlier stated, Rutter and the other named inventors on the '740 patent included in their description of the C-pepide amino acids 31-65. This description includes the dibasic amino acid residues at each end of the C-peptide.

. . .

A. "I noted the 'Catch 22' type problem that the claims as issued may be construed to cover only the natural cDNA sequence and no variations even though they cover the same resultant protein. Rutter suggest we might argue that other sequences (besides the cDNA) are functionally equivalent.

"Maybe we should consider reissuing. We only have until February '86. Rutter believes it is not practical (maybe even impossible) to make a sequence of the proinsulin size synthetically. Thus claim five may not be obvious for only that reason."

Ziemer Hartig Dep. at 181-83 (April 22, 1994).

Later, UC's concerns regarding the '740 patent were crystallized in a July 26, 1986, opinion letter to Ziemer authored by Murashige.

It appears that the issues raised by Lilly were never raised in the prosecution. It was never proposed that the generic sequence as claimed in claims 4 and 5 was made obvious by Crea in combination with known amino acid sequences. Nor was the claimed generic sequence ever asserted to have been made obvious simply by disclosure of the amino acid sequence of proinsulin, *which by applicants own admission*, already existed in the art. . . .

Lilly Ex. 3509 at 0009242-43 (emphasis added).

Finally, in a May 26, 1987, letter from Murashige to Valentin Fikovsky, manager of patent prosecution at the University's patent, trademark and copyright office, Murashige wrote:

. . .

The posture with regard to insulin, then, is that there is no prior publication describing the cloning of cDNA, although, *certainly*, the amino acid sequences for the A and B chains and *for proinsulin were known*, and certainly the existence and probably the amino acid sequence for preproinsulin also was known.

. . .

Lilly Ex. 3280 at H1495 0491 (emphasis added).

These communications convince the Court clearly that even UC recognized and accepted that the amino acid sequence for proinsulin already was in the art before the date of the application for the '740 patent. Indeed, we believe that the PTO examiner's mandated amendment in claim five was a direct result of his recognition that both fusion proteins and the amino acid sequence for human proinsulin already were in the art.

UC argues that Lilly, itself, has stated that the subject sequence was not known during the relevant time period. For this contention, UC relies on statements Lilly made to the Food and Drug Administration (FDA) in a new drug application (NDA) for PRO-Humulin. Specifically, UC argues that in the following excerpt Lilly admits UC inventors are they who determined the correct amino acid sequence:

The amino acid sequence of human proinsulin was deduced by Steiner, et al to be as shown in Figure 1. This structure was based on separate determinations of the sequence of human insulin and human C-peptide. Only small quantities [ ] of human proinsulin have ever been isolated from human pancreas. . . .*The final confirmation of human proinsulin amino acid sequence has come from sequencing of the DNA that codes for human proinsulin.* Because of the very limited

quantities of pancreatic human proinsulin that have ever been isolated, this material is not available for use as a reference standard in the chemical and physical characterization of biosynthetic human proinsulin.

UC Ex. 68 at 118 (emphasis added).

We are unconvinced that this statement is an admission by Lilly that the amino acid sequence was unknown. Preliminarily, we note that the standard for drug approval is different from the standard for patentability. *See, e.g., Application of Watson*, 517 F.2d 465, 476 [186 USPQ 11] (C.C.P.A. 1975) (holding that "Congress has given the responsibility to the FDA, not the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial market. . . ."). Thus, it would appear that statements made in one context directly are not applicable in the other context. More importantly, from the aforequoted excerpt, we glean no Lilly admission. To the contrary, Lilly, by using the phrase "final confirmation," indicates that the subject sequence previously had been confirmed by others. Indeed, expert testimony from Steiner is in accord with this position.

Steiner reasoned that the authors' use of the term "proposed" when identifying the human proinsulin amino acid sequence in the Oyer *et al.* article merely was a "fairly conservative" way of stating their conclusion. Tr. at 1512. "It certainly simply means that we believed and concluded that would be the structure of human proinsulin as we were showing it there." *Id.* Regarding the dibasic amino acid residues, Steiner testified that the authors of the article "were completely confident" that the residues were ordered in human proinsulin as the article indicated -- two arginines between the B-chain and C- peptide and one lysine and one arginine between the C-peptide and A-chain. Tr. at 1513.

In view of the evidence of record, we are convinced clearly that the amino acid sequence for human proinsulin was known to those skilled in the art as early as 1971 and surely before 1978. Again, we believe that the PTO examiner recognized this when he limited claim five to direct expression. Moreover, even if the '740 patent were not limited to direct expression, Lilly's anticipation defense would have succeeded in invalidating the broad claims of the patent -- claims five, six and eight through ten. Because we find that the amino acid sequence for human proinsulin was in the art before 1978, claim six of EPA-1929 was enabling for human proinsulin.

III. Inequitable Conduct

In the prosecution of patent applications before the PTO, patent applicants have a duty of candor, good faith and honesty. *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 [33 USPQ2d 1823] (Fed. Cir. 1995) (citing *Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co.*, 324 U.S. 806, 818 [65 USPQ 133] (1945)); see also 37 C.F.R. § 1.56 (1977). The applicant's representatives are bound by the same duty. *Id.* (citing *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 n.8 [5 USPQ2d 1112] (Fed. Cir. 1987)). "A breach of this duty constitutes inequitable conduct." *Molins PLC*, 48 F.3d at 1178.

Conduct before the PTO that may render a patent unenforceable "includes failure to disclose material information, or submission of false material information, with an intent to mislead." *J.P. Stevens & Co., Inc. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1559 [223 USPQ 1089] (Fed. Cir. 1984), cert. denied, 474 U.S. 822 (1985).

One challenging a patent as unenforceable based on inequitable conduct must prove by clear and convincing evidence that the patentee either intentionally failed to disclose

material information or intentionally submitted false material information to the PTO during the procurement of the subject patent. *Id.* Information is material if "there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." *Molins PLC*, 48 F.3D at 1179 (citing *In re Jerabek*, 789 F.2d 886, 890 [229 USPQ 530] (Fed. Cir. 1986)). Moreover, " ' [t]o be guilty of inequitable conduct, one must have intended to act inequitably,' "*Kingsdown Medical Consultants v. Hollister Inc.*, 863 F.2d 867, 872 [9 USPQ2d 1384] (Fed. Cir. 1988) (quoting *FMC Corp. v. Manitowoc Co., Inc.*, 835 F.2d 1411, 1415 [5 USPQ2d 1112] (Fed. Cir. 1987)). The Federal Circuit has recognized that " [d]irect proof of wrongful intent is rarely available but may be inferred from clear and convincing evidence of the surrounding circumstances." *LaBounty Mfg., Inc. v. United States Int'l Trade Comm'n*, 958 f.2D 1066, 1076 [22 USPQ2d 1025] (Fed. Cir. 1992) (citations omitted).

A court cannot find inequitable conduct unless a threshold level of both materiality and intent to mislead are found. *Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1439 [17 USPQ2d 1834] (Fed. Cir. 1991) (citing *J.P. Stevens & Co. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1559-60 [223 USPQ 1089] (Fed. Cir 1984), *cert. denied*, 474 U.S. 822 (1985)). If these threshold levels are satisfied, the reviewing court then must balance the two elements to determine if the patent applicant has acted inequitably. *J.P. Stevens & Co.*, 747 F.2d at 1560.

In the instant case, Lilly contends that UC acted inequitably in the procurement of both the '525 patent and the '740 patent and, thus Lilly argues, both patents are unenforceable. We turn first to address inequitable conduct in the context of the '525 patent.

A. The '525 Patent

Some background information concerning research involving recombinant DNA must precede discussion of this issue. In the early 1970's -- when experiments in the area of recombinant DNA were first contemplated -- many people, including some scientists, were concerned that such experiments might pose medical threats to humans. Tr. at 1295. The National Academy of Sciences eventually "called for a broad moratorium on all recombinant experiments until they could be . . . better reviewed by the scientific community." *Id.* At a subsequent review of recombinant DNA research in 1975, it was suggested that experiments in that area might proceed if suitable guidelines were promulgated to govern the research. *See* Lilly Ex. 3547 at HG2 580773.

Consequently, the Recombinant DNA Molecule Program Advisory Committee, previously established by the Department of Health, Education, and Welfare's National Institutes of Health (NIH), held its first meeting to develop safety guidelines. *Id.* Those guidelines were issued by the NIH on June 23, 1976, and published in the Federal Register on July 7, 1976. Tr. at 1296, 1298; Lilly Ex. 3731 at 000004; Lilly Ex. 3547. "The NIH Guidelines establish [ed] carefully controlled conditions for the conduct of experiments involving the production of [recombinant DNA] molecules and their insertion into organisms such as bacteria." Lilly Ex. 3547 at HG2 580773. For example, the regulations classified types of biological containments (i.e., plasmids) and specified which ones could be used in certain recombinant DNA experiments. The regulations also governed the type of physical containment facilities (i.e., laboratories) in which scientists could conduct

particular types of experiments.[44] The safety guidelines mandated that no plasmid could be considered to fall within an approved classification until it had been certified by the NIH Recombinant DNA Advisory Committee. Tr. at 1301.

The guidelines also stipulated that any institution receiving NIH funds was to appoint a principal investigator.[45] Under the guidelines, the principal investigator had certain responsibilities, including "supervising the safety performance of the staff to ensure that the required safety practices and techniques [were] employed" and "investigating and reporting in writing to the NIH Office of Recombinant DNA Activities and the institutional biohazards committee (or biosafety committee)[46] any problems pertaining to operation and

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[44] These regulations, however, did not pacify everyone. Public debate in Cambridge, Massachusetts about the safety of recombinant DNA research led to a determination that such research was banned from "the City of Cambridge until the citizens of Cambridge and the city council had convinced themselves that it was safe for the research to continue." Tr. at 1299. A citizens committee was appointed to investigate the matter and, in early 1977, the ban was lifted. Tr. at 1299-1300.

[45] Rutter and Goodman were co-principal investigators for the research in issue in the instant case. Lilly. Ex. 3420 at HG 002873. Rutter was then chairman of the Department of Biochemistry and Biophysics at the University of California. Tr. at 106; Lilly Ex. 3554A at 200. Goodman was then a professor in the Department of Biochemistry at the University. Tr. at 1106. During some of the time in which the subject research was being conducted, Goodman was out of the country on sabbatical leave. His absence, however, is not relevant to this discussion.

[46] An institutional biohazard committee was established in each institution that received NIH funding. According to the guidelines, such a committee was responsible for, inter alia, certifying, and recertifying annually, to NIH that the facilities, procedures, practices, training, and expertise of involved personnel had been reviewed and approved. Lilly

(continued...)

implementation of biological and physical containment safety practices and procedures, or equipment or facility failure." Lilly Ex. 3547 at HG2 580791. The guidelines governed the conduct of all NIH- supported research in the area of recombinant DNA. The research UC was conducting on rat insulin -- the research that formed the basis of the '525 patent -- was NIH-supported. Consequently, UC was to operate within the strictures of the safety guidelines.

By January of 1977, the NIH only had certified the plasmids denominated pSC101 and pCR1 for experiments with mammalian DNA. Tr. at 1301. According to Rutter, UC scientists delayed their recombinant DNA research, awaiting the NIH green light on use of a more advanced vector -- either pMB9 or pBR322. Tr. at 127. Rutter said UC representatives preferred to use pBR322. *Id.* Reportedly, that vector would be the most effective cloning agent. *Id.* On April 18, 1977, the NIH certified plasmid pMB9 as safe. Lilly Ex. 3554A at 177. On July 7, 1977, the NIH certified plasmid pBR322. *Id.*

Lilly contends that UC researchers knowingly used a plasmid not yet certified for use -- PBR322 -- in conducting its rat insulin experiments. Moreover, Lilly argues that UC researchers misrepresented the origins of their rat insulin data to the public, the NIH, the United States Senate[47] and the PTO

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[46](...continued)
Ex. 3547 at HG2 580781.

[47] Hearings before a subcommittee of the United States Senate were held in November of 1977 to examine the potential need for federal regulation governing all recombinant DNA research including research not funded by the NIH. Lilly Ex. 3554A. At the hearings, Rutter testified about the pBR322 incident. *Id.* at 200-24. Rutter told the subcommittee, *inter alia*, that the application for the '525 patent was not based on PBR

(continued...)

in order to conceal their misuse of plasmid pBR322. According to Lilly, the UC researchers' misuse of the plasmid and misrepresentations of the origins of their data are material to patentability of the '525 patent, and the misrepresentations of their data were intended to mislead the PTO. Thus, Lilly argues, a finding of unenforceability based on inequitable conduct is appropriate.

Clearly, UC's scientists used pBR322 in their research before the NIH had certified that plasmid for use. In January of 1977, working in Goodman's laboratory at the University, Ullrich began using pBR322 in his recombinant DNA experiments. Ullrich testified that he began using the plasmid after a colleague informed him by telephone that the NIH had approved pBR322 for use. Tr. at 797-98; Lilly Ex. 3420 at HG 002878. The record indicates that prior to his use of pBR322, Ullrich informed Rutter

that he had heard pBR322 was approved and that he intended to proceed with his experiments. Dr. Rutter concurred with Dr. Ullrich's plan, without further verification of the status of pBR322.

Lilly Ex. 3420 at HG 002870.

Subsequently, during a February 4, 1977, meeting, certain UC researchers -- including Ullrich and Shine -- learned that although approval of pBR322 had been recommended, the NIH director's requisite certification of the plasmid as safe had not

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[47](...continued)
322 research, *id.* at 217-18, and that there were no commercial interests motivating UC to use the uncertified plasmid. *Id.* at 219.

yet issued.[48] Lilly Ex. 3420 at HG 002871-72. Ullrich averred that he earlier had not been aware of the distinction between approval and certification. Tr. at 800. Thus, UC's premature use of pBR322 through February 4, 1977, was a violation of the NIH guidelines, but it was not necessarily an intentional violation.

The record, however, illustrates that UC researchers did not halt their use of pBR322 and/or the fruits of previous experiments with that vector after learning that pBR322 had not been certified. In fact, UC agrees that the experiments continued until at least March 3, 1977. Lilly Ex. 3420 at HG 002871. In its report to the Office of Recombinant DNA Activities (ORDA) concerning UC's premature use of pBR322,[49] UC's biosafety committee stated:

At this [February 4] gathering, the investigators in Dr. Goodman's laboratory (including Drs. Ullrich and Shine) reportedly learned for the first time that there was some confusion about the status of pBR322 . . . However, the initial cloning experiments with pBR322 and insulin cDNA had been completed, and clones had been obtained. After February 4, no new clones were constructed, but those already obtained were grown up and examined for the presence of recombinant DNA.

. . .

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[48] The record suggests that Goodman actually became aware of the uncertified status of pBR322 on March 1, 1977. Lilly Ex. 3400 at WR 10052. Reportedly, on March 4, 1977, Goodman informed Rutter of the matter. *Id.*

[49] The way in which ORDA became aware of the pBR322 incident is discussed infra at 73-74.

There is no satisfactory explanation as to why the investigators in Dr. Goodman's laboratory continued experiments with these recombinant plasmids after February 4.

Lilly Ex. 3420 at HG 002872. Moreover, when questioned at trial, Ullrich did not deny use of pBR322 after learning that it had not been certified. Tr. at 824. We find that the record clearly supports Lilly's contention that UC knowingly violated NIH safety guidelines when its researchers continued to use pBR322 in recombinant DNA experiments even after learning that the plasmid had not yet been certified for use.

Additionally, neither Rutter nor Goodman officially reported the unauthorized use of pBR322 to the NIH after the time they became aware of the prohibited use. Rather, Rutter testified that he had an informal telephone conversation with Dr. DeWitt Stetten (Stetten), NIH deputy director for science, and that he and Stetten ultimately decided against a formal disclosure of the incident. Tr. at 129-30. In fact, Rutter testified that the conversation between Stetten and himself "was carried out in a deliberate way to convey the fact, but not to create a need to disclose . . . [t]o make a formal disclosure . . . There was no formal disclosure." Tr. at 246. Rutter also testified that during the conversation, Stetten and Rutter decided that the pBR322 clones would be destroyed. *Id.* at 131. This conversation reportedly occurred sometime between March 16-19, 1977. Lilly Ex. 3420 at HG 002873.

Furthermore, neither Rutter nor Goodman informed UC's own biosafety committee of the misuse of pBR322. Rather, Dr. David Martin (Martin), then chairman of UC's biosafety committee, "heard rumors" of the incident through a technician in Rutter's lab sometime in May, 1977. Tr. at 227; Lilly Ex. 3420 at HG 002874. Martin then discussed the matter with Rutter and Goodman. *Id.* At a June 3, 1977, biosafety

committee meeting, Martin reported the UC scientists' use of pBR322. However, an examination of the minutes of that meeting indicates that the committee was not informed fully of the events that had occurred. As UC stated in its committee report to the NIH,

> [t]he failure of the Biosafety Committee to notify the NIH of the pBR322 incident was primarily a consequence of the fact that the Committee itself was unaware of the details and import of the event. On the basis of the information the Committee had at that time, it was not aware that a violation had occurred.

Lilly Ex. 3420 at HG 002874.

Thus, it is obvious that UC representatives did not formally report UC's researchers' violation of the guidelines to the NIH, nor did they provide a detailed explanation of the incident to UC's biosafety committee at its June 3, 1977, meeting. Events occurring later, however, brought the incident to the surface.

On September 9, 1977, Nicholas Wade (Wade), a *Science* reporter, called Dr. William Gartland (Gartland), director of ORDA, asking questions about UC's alleged use of an uncertified plasmid. Lilly Ex. 3731 at 000095. Wade stated that he was writing an article about the pBR322 incident -- an article that subsequently was published in the September 30, 1977, issue of the publication. *Id.* at 83, 87. Gartland apparently first learned of UC's inappropriate use of the plasmid during Wade's telephone call to him. *Id.* at 83.

On October 11, 1977, Gartland wrote Dr. James Cleaver (Cleaver), chairman of UC's biosafety committee, asking for an accounting of the incident. Lilly Ex. 3731 at 000088-89. Cleaver responded on October 25, 1977, including in his response a memorandum authored by Goodman and Rutter

detailing, as they recollected, the events surrounding the pBR322 incident. Lilly Ex. 3731 at 000090, 000092. In the memorandum, Goodman and Rutter stated that the decision was made to destroy the pBR322 clones. No date was affixed to this decision. *Id.* However, in the biosafety committee's January 20, 1978, report to the NIH -- in which the committee answered NIH questions about UC's misuse of pBR322 -- Rutter and Goodman said that Ullrich, the UC scientist actually working with the plasmid, told them that he disposed of the pBR322 clones on March 19, 1977.[50] Lilly Ex. 3420 at HG 002873.

It is clear from the record that Ullrich did not destroy all the material associated with pBR322. He saved the purified DNA associated with the use of pBR322 plasmids, and Goodman and Rutter were aware that he did. In registered letters that Rutter and Goodman testified to having exchanged during the events in issue, they admitted that they chose to " [k]eep the cloned DNA since the experiments had already been performed . . . We believed that further sequencing of the DNA clones was acceptable since the hypothetical danger, if any, is not with the DNA itself." Lilly Ex. 3361 at HG 000691-92; Lilly Ex. 3363 at WR 10720-21; *see also* tr. at 231-234, 1149-1153. Goodman's letter to Rutter was sent March 25, 1977; Rutter's letter to Goodman was sent March 22, 1977. These "smoking gun" letters could have had no purpose but to keep either of the writers from attributing the misuse to the other.

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[50] In identical letters Rutter and Goodman exchanged with each other in March of 1977, discussed *infra*, they state that on March 5, 1977, Ullrich destroyed the "plasmid containing cells and kept only the purified DNA from the clones. . . ." Lilly Ex. 3361 at HG 000691; Lilly Ex. 3363 at WR 10720.

At trial, Rutter and Goodman testified that although the letters reflect that they chose to retain the cloned DNAs, they actually chose a different course of action. They contended that they destroyed all the cloned DNAs. Tr. at 302, 1111. When asked why he and Goodman did not amend their letters to reflect a different decision, Rutter responded:

> Because actually we acted on the advice of DeWitt Stetten and destroyed the clones. It was unnecessary to adapt this guideline. We had carried out the activities which we had decided, namely, to destroy the clones for pBR322.

Tr. at 302.

We believe the registered letters are reflective of Rutter and Goodman's contemporaneous level of concern over the pBR322 incident. We are far from convinced that the two would go so far as to mail identical registered letters to one another admitting to having taken a course of action that flew in the face of NIH regulations and, subsequently, upon abandoning that course of action, permit those letters to stand uncorrected in their respective files. Moreover, the earlier of these registered letters was dated March 22, 1977. Rutter's telephone conversation with Stetten was, at the latest, on March 19, 1977. Thus, the letters were exchanged after Rutter and Goodman had time to contemplate and decide their course of action and after the time Ullrich allegedly destroyed the tainted materials. In light of the persuasive nature of the registered letters and other evidence of record, we find Rutter and Goodman's trial testimony regarding the letters not credible.

In addition, Ullrich's trial testimony indicates that Goodman and Rutter did not decide to abandon use of the pBR322 DNA clones after they learned of pBR322's uncertified status.

After Ullrich's recollection was refreshed by an examination of one of the registered letters, the following dialogue transpired:

Q. Does that refresh your recollection that you were, in fact, instructed by Drs. Goodman and Rutter to continue to work with the DNA even after you learned it was not certified?

A. I wouldn't use the word "instructed."

Q. Would you turn to Defendant's Exhibit--

THE COURT: Wait just a minute. What word would you use?

THE WITNESS: It was probably the result of a discussion and an agreement among more than Drs. Howard Goodman and Rutter.

Tr. at 829.

We find by clear and convincing evidence that UC representatives continued to use at least the fruits of the uncertified plasmid in sequencing experiments well beyond the time they learned that such use was inappropriate. The Court believes such use is tantamount to use of the plasmid itself. Next, we must determine whether UC researchers misrepresented the origins of the rat insulin data -- data on which the '525 patent is based.

On May 9, 1977, Rutter submitted to the journal *Science* a manuscript in which UC researchers described the isolation of four pieces of rat insulin DNA. Lilly Ex. 3391; Lilly Ex. 3380. The pieces of DNA isolated and sequenced were denominated in the *Science* article as pAU1, pAU2, pAU3 and pAU4. The researchers stated in their manuscript describing their rat insulin work that they had used the bacterial plasmid pMB9 in

their research efforts. Notably, pMB9 was not certified for use by the NIH until April 18, 1977.

Lilly contends that although UC researchers asserted that the work leading to the *Science* manuscript -- and, ultimately the '525 patent -- was done with plasmid pMB9, yet actually the work was done with the uncertified vector pBR322. Lilly argues that the DNA pieces described in the Science article really are those DNA clones obtained by UC's unauthorized use of pBR322. An examination of the evidence and trial testimony leads us to conclude that Lilly's position is well supported. We explain.

Ullrich maintained a laboratory notebook regarding his research activities and in that notebook he described his work with pBR322. *See* Lilly Ex. 3340. In his notebook, Ullrich specified which of the DNA clones showed a positive result from a hybridization experiment involving microorganisms transformed by the uncertified pBR322 plasmids containing rat islet cDNA. *Id.* at HG 000445; tr. at 834-37. Ullrich labelled each of the clones for identification purposes. Tr. at 835-37. Significant to this discussion are the clones he labelled 1-13, 3-9 and 3-10.

Reference to these same clone numbers, i.e., 1-13, 3-9 and 3-10, was found on certain pages contained in a folder designated "INSULIN expt" from Howard Goodman's files. *See* Lilly Ex. 3354 at HG 002075. Ullrich admitted that the numbers 1-13, 3-9 and 3-10 "match with the numbers that we had seen before on the hybridization experiment." Ullrich further testified that several of the pages found in this folder contained his handwriting. Tr. at 840-41. He also agreed that the page in this folder entitled "Summary of Insulin Clones" includes a diagram that describes where the pieces of DNA from pBR322 started and stopped. Tr. at 841.

At trial, Gilbert, in his expert testimony, relied on Ullrich's lab notes, the insulin experiment folder from Goodman's files, and a handwritten manuscript draft describing an experiment conducted in the plasmid pBR322.[51] *See* Lilly Ex. 3365. Gilbert compared the sequence data from the unauthorized pBR322 research work with the sequence data reported in the *Science* article and concluded that the pieces of DNA reported in the article were derived from pBR322 research. Tr. at 1308, 1310-33. He stated that clone pAU-1 listed in the *Science* article contained the same starting and stopping points as pBR322 clone 1-13; pAU-2, the same as pBR322 clone 3-9; and pAU-3, the same as pBR322 clone 3-10. *Id.* Moreover, Gilbert testified that pAU-4 identified in the Science article corresponds to other sequence data reported in the pBR322 research. Tr. at 1321-22.

Gilbert was asked whether a second experiment, conducted in the same way as that with pBR322, likely would result in the isolation of clones having the same structure. Tr. at 1332. Gilbert answered that a researcher might isolate another clone having the same structure as that identified as 3-9. Tr. at 1333-34. However, he added that the same was not true

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[51] Gilbert also relied on Goodman's notes of a March 14, 1977, meeting with Lilly. Tr. at 1315-16; Lilly Ex. 3349. At this meeting, Goodman had drawn on the board a plasmid labeled in the same fashion as one in Goodman's insulin experiment folder. Lilly Ex. 3349 at HG 001462. In the experiment folder, the drawing appears under the title, "clone 1-13." Lilly Ex. 3354 at HG 002081. The Goodman- Lilly meeting was on March 14, 1977. Hence, Gilbert concluded that the sequence listed in Goodman's insulin experiment had to exist before that date. Because Rutter testified that UC experiments with plasmid pCR1 were ineffective, tr. at 137, and because pMB9 was not even certified for use until April 18, 1977, the sequence described in Goodman's insulin experiment folder, and later drawn on the board at the Lilly meeting, had to be a pBR322 sequence. Tr. at 1328.

of clones 1-13, 3-10 or that identified as pAU-4 in the *Science* paper. *Id.* In these fragments, one would have expected variations in other experiments. *Id.* Even Ullrich declared it highly unlikely that the sequence reported in pAU-4 would be duplicated by random chance. Tr. at 873-74. UC expert Richards concurred with Ullrich's observation. Tr. at 206.

The Court finds Gilbert eminently qualified and credible. Significantly, we find that the evidence supporting his interpretation of the sequence of events is clear and convincing.[52] Hence, we find that the duplications in the structure of pBR322-derived clones and the structure of clones reported in the *Science* manuscript and the original '525 patent application are not products of random chance. Rather, we find that UC researchers used data derived from the pBR322 experiments in the aforementioned publications.

The Court also believes that comment on Rutter's testimony before the Senate subcommittee in November of 1977 is in order. After comparing the evidence of record against that testimony, we find that Rutter was not candid with members of

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[52] At trial, Lilly introduced certain drafts of research manuscripts found in UC's files. Lilly contends that although these manuscripts purport to arise from research conducted with certified plasmids, yet the data contained therein illustrate that the manuscripts actually were based on work done with the uncertified vector pBR322.

We agree with Lilly that the record illustrates that the data contained in these manuscripts originated in pBR322 research work. However, we already have found that the research work reported in the *Science* article and, ultimately, in the '525 patent, is based, at least in part, on work done in the uncertified plasmid. Thus, while the common threads in these manuscripts (e.g., identical sequencing errors, identical typographical errors) strengthen Lilly's argument that the manuscripts all rely upon pBR322 research work, a detailed explanation of those documents and their corresponding features is unnecessary for purposes of this decision.

the subcommittee. For example, Rutter testified that the experiments with the uncertified plasmid were not spurred by commercial interests. Lilly Ex. 3554A at 219. Rutter also averred that none of the work in the plasmid had any relationship to Genentech, Inc. (Genentech).[53]

Certain evidence of record counters Rutter's averments. The evidence indicates that UC representatives began collaboration discussions with both Genentech and Lilly shortly after learning that rat insulin DNA had been isolated in the uncertified pBR322. For example, on March 9, 1977 -- eight days after learning of UC's misuse of the plasmid and seven days after learning that an insulin clone actually had been obtained from pBR322 work -- Goodman contacted Lilly. Lilly Ex. 3400 at WR 10052. In his notes recording that conversation, Goodman wrote: "Have rat clone. Q. How? A. Don't want to say too much now, but can prove it." Lilly Ex. 3343A. Goodman met with Lilly personnel on March 14, 1977. Lilly Ex. 3349. In his notes of that meeting,[54] Goodman wrote that he discussed a plasmid but that when someone asked him what plasmid, he answered, "Can't say."*Id.* at HG 001462. Additionally, Goodman's notes reflect that he told those present that what he wanted in exchange for what he had to offer included "money for lab" and "consulting."*Id.* at HG 001465.

Other evidence indicates that Goodman also approached Genentech during the same time period. On March 12, 1977, he met with Genentech representatives; Goodman's handwritten

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[53] Genentech, a corporation located in California, is involved in other of the six cases consolidated in this Court for pretrial proceedings by the Judicial Panel on Multidistrict Litigation. See, supra at 1-2.

[54] At trial, Goodman verified that the notes were in his handwriting. Tr. at 1219.

notes of that meeting indicate that Genentech offered Goodman "money for salaries, supplies, equipment, shares (common) . . . [and] consulting for me." Lilly Ex. 3347 at HG 001355. The record illustrates that Goodman called Genentech representative Ron Swanson at home the following day. Lilly Ex. 3348 at HG 001357. Goodman's notes of that telephone conversation state that Goodman "[h]inted [at] we were bringing something very valuable to the co & should be compensated for -- difference in kind between 'idea' & 'having [it]."*Id.* at HG 001357. Subsequently, other handwritten notes by Goodman illustrate that on March 15, 1977, he again called Genentech and reported the following: "Problem that in Boyer plasmid. Lay low. Not approved. Can't apply for patent yet." [55] Lilly Ex. 3351 at HG 001364.

Significantly, although at trial Goodman could not recall when Rutter became involved in the Genentech negotiations, he did not dispute that Rutter did become involved. In fact, in Goodman's deposition of May 18, 1993, he testified that while Rutter was not present at the first of the Genentech negotiation meetings that he could recollect, Rutter was involved in all subsequent meetings. Tr. at 1237-38. Hence, contrary to Rutter's statements to the Senate subcommittee, we find that continued use of the fruits of the pBR322 research was driven

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[55] Evidence of record convinces us that Goodman was referring to pBR322 when he named the "Boyer plasmid." Ullrich testified that scientists in Herb Boyer's laboratory developed pBR322. Tr. at 797-98. Moreover, other testimony reveals that the only plasmid with which UC researchers had achieved success by March of 1977 was the uncertified pBR322. Specifically, Rutter averred that UC was unsuccessful in its attempts to clone in plasmid pCR1. Tr. at 137. Furthermore, Rutter stated that UC researchers did not begin using vector pMB9 until after it was approved by the NIH. Tr. at 136. That approval was not received until April of 1977. Consequently, Goodman's mid-March 1977 reference to "Boyer plasmid" must mean pBR322.

by commercial interests and we find that those commercial interests were tied closely to Genentech.[56]

UC asserts that even if the Court determines that the sequence data in issue did stem from work done in the uncertified plasmid pBR322, Lilly still cannot succeed in its inequitable conduct charge. Specifically, UC argues that Lilly cannot prove by clear and convincing evidence not only that UC's act was material to the prosecution of the '525 patent, but also that UC representatives committed the act with an intent to deceive the PTO examiner.

In *General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405 [30 USPQ2d 1149] (Fed. Cir. 1994), the patent applicant, Samick, sought expedited examination of its application because, Samick alleged, the claimed design was being infringed. *Id.* at 1406. In order to obtain expedited examination, Samick had to file a "petition to make special." *Id.*

At the time Samick filed its petition, the MPEP [Manual of Patent Examining Procedure] required that an applicant support a petition to make special with an oath or declaration alleging facts showing, among other things, "that he or she had made or caused to be made a careful and thorough search of the prior art or has a good knowledge of the pertinent prior art."

Id. (quoting MPEP Section 708.02, II(5)). In light of this requirement, Samick, through its attorney, submitted a declaration stating that a prior art search had been conducted.

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[56] It also is interesting to note that by agreement with UC the inventors are entitled to 50 percent of the net profits derived from any royalties or fees received from patent rights.

However, a jury determined that, contrary to Samick's attorney's declaration, Samick had not conducted a prior art search and, thus, that Samick intentionally had made a material false statement to the PTO. *Id.* at 1407. The Court entered judgment against Samick based on inequitable conduct rendering its patent unenforceable. *Id.* at 1408. The Federal Circuit affirmed. *Id.*

We believe the decision in *Samick* illustrates that the Federal Circuit's application of the concept of inequitable conduct is not limited to situations in which the patent applicant intentionally misleads the PTO in the context of prior art. Rather, inequitable conduct may be found in a variety of circumstances in which the patent applicant has abandoned his duty of candor, good faith and honesty to the PTO.

We already have determined that certain of the data found in the '525 patent was the result of an experiment conducted in the uncertified pBR322 plasmid. Moreover, in its prosecution of the '525 patent, UC failed to report its use of that vector to the PTO examiner but rather reported use of pMB9 for the data in issue. In light of these findings, the Court must determine whether UC's misrepresentation to the PTO was material to the patentability of the '525 patent.

After considering the facts and the law, we find that there is a substantial likelihood that a reasonable examiner would have considered UC's unauthorized use of pBR322 important in his patentability determination. UC, as an institution that accepted funding from the NIH, was obligated to follow the guidelines issued by that agency; UC was aware of its obligation. Even after UC representatives admittedly learned of their premature use of the subject plasmid, they, nonetheless, continued, at the very least, to use the sequence data they secured from their tainted research. A reasonable examiner easily could have

determined that without use of the unauthorized plasmid and the data therefrom, UC's application for the '525 patent would not have acquired its May 27, 1977, file date. Indeed, it is impossible to determine whether UC would have been the first to make patent application had its representatives followed the rules to which its competitors were bound.

The Court also must consider the issue of intent, though the issue need not detain us long. First, we consider UC's forbidden use of pBR322 long past its recognition of the uncertified status of that plasmid. Second, we reiterate our determination that UC representatives incorporated pBR322 data into the '525 patent application -- an incorporation that was not accompanied by candor or honesty in UC's prosecution of the '525 patent application. Considering the admissions contained in the exchange of letters between Rutter and Goodman, we find no room for doubt that UC's failure to reveal its unauthorized use of pBR322 was intentional. Moreover, the Court finds that such intentional failure necessarily was meant to deceive or mislead the PTO examiner. UC was aware of its violation of the NIH safety guidelines and apparently was concerned that the PTO would endorse neither its experimental use of uncertified pBR322 nor its use of the results of that experiment in the '525 patent application.

The United States Supreme Court has stated that

. . . a patent is an exception to the general rule against monopolies and to the right to access to a free and open market. The far-reaching social and economic consequences of a patent, therefore, give the public a paramount interest in seeing that patent monopolies spring from backgrounds free from fraud or other inequitable conduct and that such monopolies are kept within their legitimate scope.

Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co., 324 U.S. 806, 816 [65 USPQ 133] (1945). We are persuaded that endorsement of UC's conduct by enforcing the '525 patent would counter the public's interest. Hence, we hold that the '525 patent is unenforceable based on UC's inequitable conduct.[57]

B. The '740 Patent

Lilly contends that UC failed to disclose material prior art during its prosecution of the '740 patent, intending to deceive the PTO examiner. Similar to its preceding argument, Lilly asserts that such failure counters UC's duty of candor, good faith and honesty to the PTO, rises to the level of inequitable conduct, and renders the '740 patent unenforceable. [58]UC argues that the allegedly withheld prior art reference was, at most, cumulative; that UC did not intend to deceive the PTO examiner; and, hence, that UC did not procure the '740 patent inequitably.

Lilly's inequitable conduct charge arises from UC's failure to cite to the PTO examiner a European patent application (EPA-1929), which was filed November 6, 1978 and published on May 16, 1979 -- prior to the September 12, 1979, file date

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[57] Lilly contends that UC's inequitable conduct in procurement of the ' 525 patent should render the '740 patent unenforceable as well. However, we believe UC acted inequitably in the prosecution of the '740 patent itself, as discussed *infra*. Therefore, we need not consider whether UC's conduct associated with the '525 patent should hinder its ability to enforce another patent in suit.

[58] Lilly brought this issue before the Court previously in its third motion for summary judgment. In an Entry deciding that motion, we concluded that summary resolution of Lilly's allegations of inequitable conduct in the context of the '740 patent prosecution would be improper.

of the '740 patent. The disclosure of EPA-1929 was based on the work of Dr. Keiichi Itakura (Itakura) and Dr. Arthur Riggs (Riggs) and was embodied in other references as well. For example, the Itakura and Riggs disclosure also was contained in United Sates Patent Application Serial Number 849,692, filed by Itakura and Riggs on November 8, 1977. This application was embellished in November of 1979, and finally issued on November 3, 1987, as United States Patent Number 4,704,362 (the '362 patent).[59]

First, we must determine if the disclosure of EPA-1929 was material and not merely cumulative in the prosecution of the '740 patent. In our discussion at pages 46 through 65 of this Opinion concerning the issues of anticipation and enablement, we held that EPA-1929 was highly material to the prosecution of the '740 patent. In fact, we determined that the disclosure in EPA-1929 and its claim to human proinsulin make it impossible for the claims in the '740 patent to be interpreted as broadly as UC has urged.

We are convinced that certain of UC's arguments for patentability of the '740 patent application were contradicted by EPA-1929. Specifically, UC contended that the prior art cited by the PTO examiner actually taught away from the claimed invention because it did not suggest use of DNA encoding human proinsulin. UC. Ex. 3 at A000156, A000160. In a March 31, 1981, rejection of the '740 application, the examiner reasoned that the claims to proinsulin- encoding DNA were unpatentable in view of several publications. *Id.* at A000142.

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[59] The original United States application included techniques for chemically synthesizing DNA and a specific claim to DNA constructions containing a gene for human proinsulin. The November 1979 embellishment added to the patent application examples describing the separate A- and B- chain insulin work.

Relevant to this discussion, the examiner cited an article authored by Crea et al., outlining the work of Itakura and Riggs wherein the scientists describe construction of synthetic DNA for the A- and B-chains of human insulin in separate plasmids. *Id.* at A000142, A000145; Lilly Ex. 3100.

UC responded to the examiner's rejection, arguing that

> Crea et al teaches an entirely different approach to the synthesis of human insulin. That approach is to prepare separate and distinct transfer vectors comprising segments coding for the A chain and for the B chain. . . . That approach teaches away from the cloning of a single deoxynucleotide sequence coding for proinsulin.
>
> . . .
>
> The claimed preproinsulin and proinsulin cDNAs have utility in entirely different processes for the synthesis of human insulin, using an approach not taught or suggested by Crea et al., or any of the cited references. . . .

UC Ex. 3 at A000156, A000160.

UC appears correct in its assertion that none of the cited references suggested the approach of the '740 patent application. However, it is the uncited EPA-1929 that presents the problem. We find that EPA-1929 describes the very approach UC denied existed in any of the cited prior art. Not only does EPA-1929 describe the application of DNA synthesis techniques to human proinsulin DNA in a single plasmid, but, as we earlier noted, it actually includes a claim to a plasmid containing human proinsulin made in this fashion. *See* Lilly Ex. 3047. Consequently, we cannot find that EPA-1929 was merely a cumulative reference.

Neither do we believe that UC was unaware of EPA-1929's materiality to prosecution of the '740 patent application. First, UC was informed through a January 2, 1980, 61-page evaluation by the law firm of Irons and Sears (the Irons opinion)[60] that, in the author's view, the disclosure of EPA-1929 rendered the claims of the '740 patent *prima facie* unpatentable. See Lilly Ex. 3476 at 23847.

Second, the materiality of EPA-1929 to the examination of the '740 patent application was made clear to UC in the prosecution of foreign counterparts to the '740. UC filed a European patent application on September 11, 1980, which application corresponded to the United States application for the '740 patent. Lilly Ex. 3087. Additionally, UC filed corresponding applications in various countries, including France, Israel, Australia and New Zealand. See Lilly Exs. 3079, 3092A, 3089B, 3093B.

Sometime shortly after January 21, 1981, Lorance Greenlee (Greenlee), a Keil & Witherspoon attorney who was prosecuting the '740 patent for UC,[61] received a copy of a search report pertaining to the European patent application that corresponded to the '740 application pending in the United States.[62] Lilly Ex. 3064. The report, issued by the European

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[60] This evaluation is entitled "Evaluation of the United States Patent Position of the University of California With Respect to DNA Recombinant Technology."

[61] Greenlee was an attorney with the law firm Irons and Sears when he first began patnet work for the University of California. Tr. at 909. He continued that work at Keil & Witherspoon. *Id.*

[62] Greenlee testified that during the time he was responsible for the University's United States prosecution work, he corresponded with UC'S

(continued...)

Patent Office (EPO), informed the reader of documents considered by the EPO to be relevant to the prosecution of the European counterpart of the '740 patent application. Lilly Ex. 3091. The European report categorized the documents reported according to their level of relevancy. The search report in issue listed several documents. Significantly, EPA-1929 was categorized as particularly relevant -- the category used in European search reports to earmark a document of highest relevancy. *Id.* The search report specifically indicated that claim six -- the claim directed at human proinsulin -- was among the claims in EPA-1929 that were highly relevant to the '740 patent application's foreign counterpart. *Id.* Moreover, EPA-1929 was deemed more relevant in this search report than two documents that not only surfaced in the same search report but also were cited by UC during prosecution of the '740 patent application. Lilly Exs. 3000, 3091; tr. at 970-74.

In addition, at trial Lilly illustrated the following sequence of events. In January of 1983, Keil & Witherspoon was informed that a New Zealand counterpart of EPA-1929 had been cited against the New Zealand counterpart of the '740 patent application. PX 488 at 16611-12, 16615-17; tr. at 438-39. In April of 1983, Keil & Witherspoon was advised that EPA-1929 had been cited as particularly relevant against the French version of the '740 patent. Lilly Ex. 3080; tr. at 440-41. In June of the same year, Keil Witherspoon was notified that the German counterpart of EPA-1929 had been cited against the Israeli version of the '740 patent application. Tr. at 441-42. In August of 1983, Keil & Witherspoon was advised that EPA-1929 had been cited against the Australian version of the

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[62](...continued)
then patent administrator Roger Ditzel (now deceased), and with the inventors of the patents. Tr. at 1024.

'740 patent application. Tr. at 443-44. None of UC's foreign applications succeeded.

Significantly, the Manual of Patent Examining Procedure (MPEP) effective during UC's prosecution of the '740 patent application contained a section entitled "Prior Art Cited in Related Foreign Applications." That section read as follows:

Applicants and other individuals as set forth in Section 1.56, have a duty to bring to the attention of the Office any material prior art or other information cited or brought to their attention in any related foreign application.

Manual of Patent Examining Procedure, Section 2001.06(a) (Revised 4th ed. 1980). Despite this rule and the many repeated notifications that EPA-1929 was material, UC representatives continued to prosecute the '740 patent application without citing EPA-1929 to the PTO examiner. Greenlee testified on direct examination that he could not recall considering the relevancy of EPA-1929 in the prosecution of the '740 patent application. Tr. at 931. On cross examination, Greenlee averred that he could not recollect why he did not cite EPA-1929 to the examiner. Tr. at 983. In fact, a perusal of Greenlee's trial testimony indicates that Greenlee's present recollection regarding any one of the issues about which he was cross-examined was poor to put it charitably. See tr. at 933-1033.

Greenlee's inability to recollect relevant subject matter, however, does not lessen the impact of the paper evidence clearly illustrating that Greenlee was aware of the text of EPA-1929 by late 1979. See Lilly Exs. 3449, 3450, 3452, 3453, 3458. Moreover, all information Greenlee had acquired from other patent experts at that time indicated that a high level of materiality linked EPA- 1929 to the '740 patent application.

Indeed, the plain language of EPA-1929 included a claim to human proinsulin. Lilly Ex. 3047 at claim six. The Court thus finds that UC representatives were aware that EPA-1929 was highly material to the prosecution of the '740 patent application.

With this materiality analysis behind us, we must consider the issue of intent. Lilly contends that EPA-1929's high level of materiality compels an inference of intent to mislead.

No single factor or combination of factors can be said always to *require* an inference of intent to mislead; yet a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish "subjective good faith" sufficient to prevent the drawing of an inference of intent to mislead. A mere denial of intent to mislead (which would defeat every effort to establish inequitable conduct) will not suffice in such circumstances.

FMC Corp., 835 F.2d at 1416.

We find that the facts of this case direct that we draw an inference of intent to mislead. First, we reiterate EPA-1929's high level of materiality. Indeed, under UC's proposed interpretation of the claims in issue, EPA-1929 was "but for" material. Even under the Court's interpretation of the claims -- an interpretation that limits the claims to plasmids coding for direct expression -- there is more than a substantial likelihood that a reasonable examiner would have considered EPA-1929 important in a patentability determination of the '740 application. This is particularly so in view of the '740's prosecution history.

Specifically, the language UC originally used in claims two and five undoubtedly would have warranted the broad reading UC advocates. Original claim two claimed

[a] DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin.

UC Ex. 3 at A000036. Original claim five claimed

[a] DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin comprising a plus strand having the sequence:

[selected from among all possible DNA sequences encoding human proinsulin].

Id. at A000037. Lilly expert Armitage testified that claims two and five initially were "essentially identical claims. . . ." Tr. at 1741. We agree with Armitage's conclusion.

Importantly, the proposed broad language of claim five was not narrowed until June of 1983, when the PTO examiner mandated such amendment before allowing issuance of the '740 patent. UC Ex. 3 at A000254. Up until that time, UC had been prosecuting its '740 patent application -- an application that necessarily encompassed claim six of EPA-1929 -- without citing EPA-1929 to the PTO examiner.

UC argues that its evidence of subjective good faith effectively overcomes Lilly's allegations of intent to mislead. Specifically, UC asserts, its provocation of an interference proceeding between the Itakura and Riggs disclosure and another of UC's patents being prosecuted during the relevant time period is evidence of UC's lack of intent to deceive. UC posits that because the same examiner was handling both the

interference proceeding and the prosecution of the '740 patent, UC could not be intending to mislead the examiner. Moreover, UC contends that the dates on certain of the evidence Lilly offered at trial indicates that many of the documents on which Lilly relies for its inequitable conduct charge predate the prosecution of the '740 patent. UC opines that because the correspondence was transmitted before the prosecution of the '740, the matters contained therein could not be associated with the ' 740 patent.

UC's arguments countering intent to mislead are not sufficient to overcome EPA- 1929's high level of materiality and the evidence of record clearly illustrating that UC knew of that materiality. Preliminarily, we note that UC's provocation of the interference proceeding played a role in the Court's earlier denial of summary judgment on the issue of inequitable conduct. However, trial presented the Court with an opportunity to hear all the evidence; to determine the issue of materiality; and to judge the credibility of the witnesses. With this background, we now find that UC's provocation of an interference proceeding involving the Itakura and Riggs disclosure does not have the significance UC urges. We are unconvinced that bringing that disclosure to the attention of the PTO examiner in the context of a *different* patent application somehow justifies UC's failure to bring the disclosure to the attention of the PTO examiner in the context of the '740 patent application. Certainly, one could readily draw the inference that UC representatives pitted the Itakura and Riggs reference against a different patent application in an attempt to divert the examiner's attention from the relationship between the '740 application and the Itakura and Riggs disclosure.

UC's second offering of evidence on the issue of subjective good faith fares no better. It is true, as UC recognizes, that some of the evidence Lilly offered on the issue of inequitable

conduct predates the file date of the '740 patent application. Greenlee testified that he could not remember having received any information from UC pertaining to the cloning of human proinsulin prior to July 18, 1979; some pieces of the correspondence Lilly offered into evidence are dated in June of 1979.

For purposes of this discussion, we assume that Greenlee's testimony is accurate and that his written request for, *inter alia*, a copy of EPA-1929 initially was not spurred by UC's ensuing application for the '740 patent. Nonetheless, we cannot overlook the fact that Greenlee received EPA-1929 in late June of 1979 -- less than one month before his acknowledged receipt of information related to the '740 patent application. Moreover, given the clarity of the language of EPA-1929's claim six -- in which the inventors claim human proinsulin -- it is inconceivable that Greenlee, or other UC representatives to whom a copy of EPA-1929 was forwarded, did not shortly thereafter connect this claim with the material ultimately submitted in the '740 patent application. More importantly, the fact remains that UC representatives repeatedly were advised of the significant link between EPA-1929 and the '740 patent application after prosecution of the latter had begun. Consequently, we are not persuaded that UC sufficiently has proved subjective good faith in its effort to counter Lilly's clear and convincing evidence of intent to mislead. The Court finds that UC's inequitable conduct in the prosecution of the '740 patent renders that patent unenforceable.

IV. Conclusion

In sum, we find that Lilly infringes neither the '525 patent nor the '740 patent; that the '525 patent's claims to the mammalian and vertebrate genera and to the human species are invalid for lack of an enabling disclosure; that were we to

accept UC's offered interpretation of the broad claims in the '740 patent (an interpretation we have rejected), those claims would be invalid as anticipated; that the '525 and '740 patents are unenforceable based on UC's inequitable conduct. Judgment will be entered this day in accordance herewith.

Dated this 11th day of December, 1995.

/s/ S. Hugh Dillin, Judge
S. Hugh Dillin, Judge